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Determinants of left ventricular function one year after cardiac transplantation

COLIN J REID, MAGDI H YACOUB
From Harefield Hospital, Middlesex

SUMMARY Left ventricular systolic function was assessed by radionuclide angiography in 107 consecutive transplant recipients who were alive one year after operation. Mean (SEM) ejection fraction was 62·4 (4·6) at rest and 68·8 (5·4) on exercise. The influence of donor-related factors (donor age and sex, ischaemia time), recipient-related factors (recipient age and sex, frequency of acute rejection), type of immunosuppression (cyclosporin/azathioprine or prednisolone/azathioprine), and frequency of hypertension on left ventricular function one year after operation was examined by univariate and multivariate analysis. There was a close association both at rest and on exercise between a higher ejection fraction and treatment with cyclosporin/azathioprine. There was a trend for lower donor and recipient age, shorter ischaemia time, and fewer rejection episodes to be associated with better left ventricular function, but this was not statistically significant.

Left ventricular systolic function was well maintained in most patients a year after cardiac transplantation. The type of immunosuppression used had a strong influence on the left ventricular systolic function of the transplanted heart.

Cardiac transplantation has become established as an effective form of treatment for patients with severe myocardial disease. The one year survival is 75–92%[1-4] and the quality of life of most of these patients is good. The late results of the operation are as yet not known. One of the main factors determining the longer term outcome of transplantation is left ventricular function, which can be influenced by several factors related to the donor or recipient or to the type of immunosuppression used.

We have examined left ventricular function one year after transplantation and have assessed the possible influence of some of these factors.

Patients and methods

STUDY GROUP

We studied 107 consecutive recipients who were alive one year after transplantation and who had undergone operation between February 1980 and December 1984 (fig 1). Four patients were not available for study because they lived abroad. There were 101 men, and the age range of the group at the time of operation was 12–59 (mean 44·1) years. An orthotopic operation had been performed in 93 (87%) patients and a heterotopic one in 14 (13%).

During this period, 155 patients had cardiac transplantation. There were 44 early (<1 year) deaths, 19/39 (48·7%) of those receiving prednisolone and azathioprine and 25/116 (21·5%) of those on cyclosporin/azathioprine. The late mortality was 9/20 (45%) in the prednisolone and azathioprine group (follow up 15–88 (mean 49·5) months) and 4/91 (4·4%) in the cyclosporin and azathioprine group (follow up 22–57 (mean 36·6) months).

RADIONUCLIDE VENTRICULOGRAPHY

Left ventricular function was assessed by measurement of ejection fraction with gated radionuclide cineangiography at rest and on exercise. Red blood cells were labelled in vivo with 15 mCi technetium-99m. Images were acquired with an all purpose parallel-hole collimator and a gamma scintillation camera (Ohio-Nuclear). Studies were performed with the patient at rest in the supine position in a 40° left anterior oblique projection. Symptom limited exercise was performed in a semi-supine position on a bicycle ergometer with an initial

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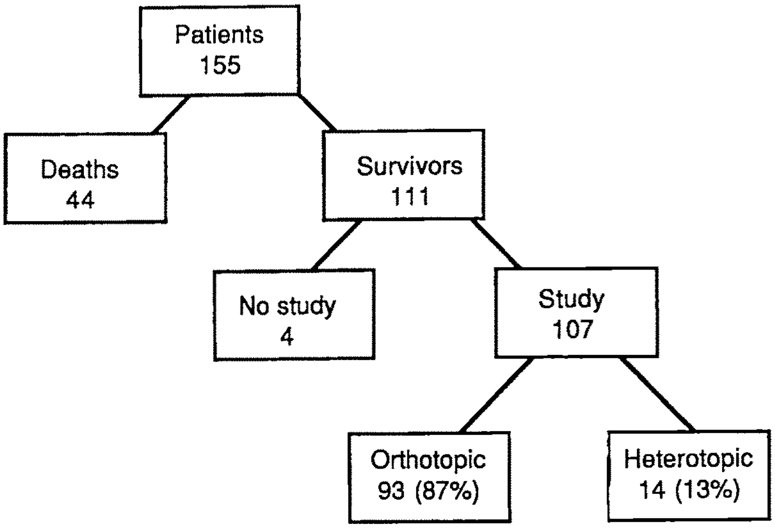

Fig 1 *Study population of patients who had cardiac transplants between February 1980 and December 1984.*

workload of 25 W and data were acquired over 10 minutes once a steady state had been reached. The ejection fraction was calculated by the multiple regions of interest method with computer-determined background areas. Exercise studies were not performed in heterotopic recipients in view of the difficulty in obtaining reliable electrocardiographic gating of the donor heart.

VARIABLES

Donor related

Donor age and sex.—Figure 2 shows the age distribution of the donors. Donors were aged from 9 to 40 (mean 21·7) years. There were 50 (47%) donors below the age of 20, 38 (35%) between 20 and 30, 18 (17%) between 30 and 40, and 1 (1%) aged 40. Seventy nine (74%) were male and twenty eight (26%) female.

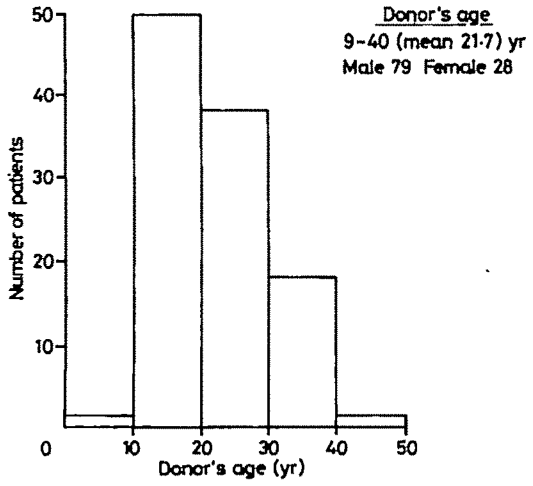

Fig 2 *Distribution of ages of donors.*

Ischaemia time.—The duration of the ischaemia time, defined as the time between clamping of the donor aorta and reperfusion of the donor heart in the recipient, varied from 70 to 300 (mean 138) minutes.

Table 1 shows the variation in ischaemia time.

Recipient related

Recipient age and sex.—The age range of the recipients was 12–59 (mean 44·1) years (fig 3). Eighty five (79%) patients were aged ≥40 years at the time of transplantation. One hundred and one (94%) recipients were male.

Acute rejection.—Table 2 shows the number of episodes of acute rejection in each patient in the first year after operation. A rejection episode was defined as one during which an endomyocardial biopsy

Table 1 *Distribution of ischaemia time of donor hearts*

Ischaemia time (min)	*No donors (%)*
60– 90	7 (6)
90–120	36 (34)
120–150	25 (24)
150–180	15 (14)
180–210	12 (11)
210–240	8 (7)
240–300	4 (4)

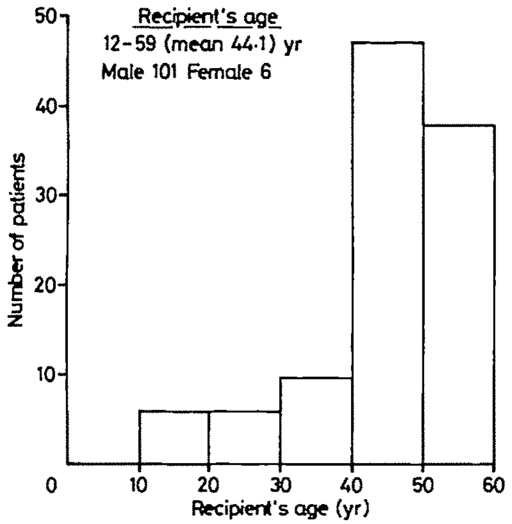

Fig 3 *Distribution of ages of recipients.*

specimen showed infiltration of interstitial, perivascular, or endocardial pyroninophilic mononuclear cells with or without myocytolysis. Patients were treated with methylprednisolone (1 g daily) for three days and/or antithymocyte globulin. The mean number of rejection episodes per patient during the first year after operation was 2·7.

Immunosuppression

A combination of oral steroids (prednisolone 1·5 mg/kg/day, reducing to 0·5 mg/kg/day) and azathioprine (2 mg/kg/day) was used as immunosuppression in the first 19 (18%) patients in this study.

The next 88 (82%) patients were given a combination of cyclosporin (5–20 mg/kg/day) and azathioprine (2 mg/kg/day). Oral steroids were not routinely used in these patients.

Hypertension

Hypertension was defined as a blood pressure reading ≥145/90 on two or more occasions during the first year. In the prednisolone and azathioprine group 2/19 (11%) were hypertensive and in the cyclosporin and azathioprine group 24/55 (44%) were hypertensive.

Myocardial preservation

St Thomas' cardioplegic solution, 20 ml in 1 litre of normal saline introduced into the aortic root, was used for donor heart preservation in all cases. The hearts were then transported in Hartmann's solution at 4°C.

Table 2 *Occurrence of acute rejection in first year after transplantation*

No of episodes	*No of patients*	%
0	10	9
1	20	18
2	17	16
3	35	33
4	6	6
5	11	10
6	6	6
7	1	1
8	1	1

Statistical analysis

Data were analysed by simple and multiple linear regression. The regression coefficient was obtained and p value was determined. $P < 0.05$ was regarded as significant.

Results

LEFT VENTRICULAR FUNCTION

The distribution of ejection fraction in the study group at rest (fig 4) and on exercise (fig 5) is shown. The ejection fraction was 60% in 75 (70%) patients at rest and 79% patients on exercise. Left ventricular function was impaired (ejection fraction <50%) in 12 (11%) patients at rest and three patients on exercise.

The mean (SEM) ejection fraction in a group of normal volunteers in our laboratory was 63 (3·0) % at rest and 71 (2·3) % on exercise. Pooled data on ejection fractions in the normal population from 28 centres world wide gave a value of 62·3 (6·1) % at rest and 70·3 (7·6) % on exercise.[5]

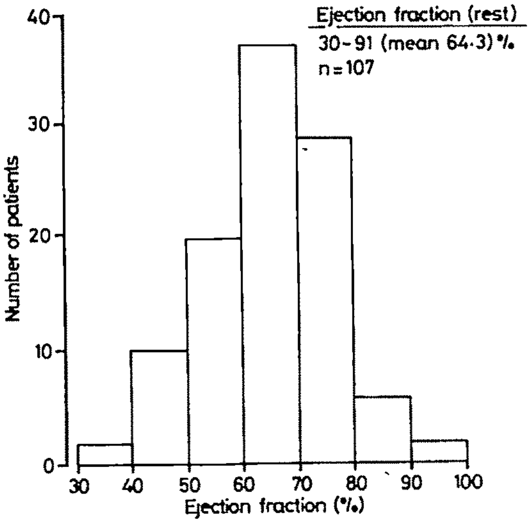

Fig 4 *Range of ejection fraction of study group at rest.*

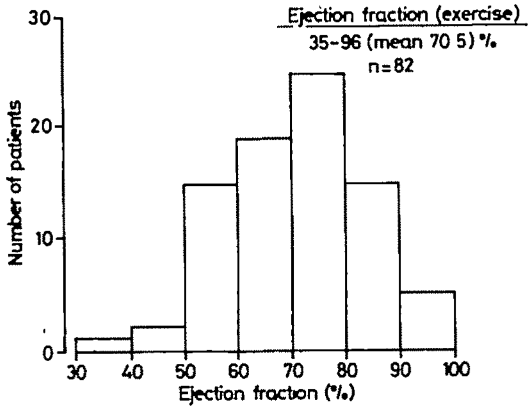

Fig 5 *Range of ejection fraction of 82 patients undergoing exercise studies.*

UNIVARIATE ANALYSIS (TABLE 3)

There was a significant association between treatment with cyclosporin and azathioprine and a higher ejection fraction at rest ($p<0\cdot01$) and on exercise ($p<0\cdot001$). Greater recipient age was associated with a lower ejection fraction at rest ($p<0\cdot01$) but not on exercise.

There was a trend for lower donor age, smaller number of rejection episodes, and shorter ischaemia time to be associated with improved ejection fraction both at rest and on exercise but the 95% confidence limit for this trend was not statistically significant.

MULTIVARIATE ANALYSIS (TABLE 4)

With multivariate analysis the association between treatment with cyclosporin/azathioprine and higher ejection fraction at rest and on exercise persisted ($p<0\cdot05$ and $p<0\cdot01$ respectively). No significant association was demonstrated between resting or exercise ejection fraction and the other variables.

Table 3 *Evaluation of influence of variables on rest and exercise ejection fraction by univariate analysis*

	Regression coefficient	*t value*	*p*
	Rest		
Cyclosporin	7·84	2·71	< 0·01
Recipient's age	−0·25	−2·31	< 0·01
Donor's age	−0·28	−1·70	< 0·10
Acute rejection	−1·05	−1·61	< 0·50
Donor's sex (M)	−3·40	−1·34	< 0·50
Ischaemia time	−0·16	−0·66	> 0·50
Recipient's sex (M)	2·39	0·48	> 0·50
	Exercise		
Cyclosporin	11·51	3·46	< 0·001
Recipient's age	−0·08	−0·60	> 0·50
Donor's age	−0·29	−1·38	< 0·50
Acute rejection	−1·05	−1·37	< 0·50
Donor's sex (M)	2·30	0·73	> 0·50
Ischaemia time	−0·03	−0·86	< 0·50
Recipient's sex (M)	1·41	0·24	> 0·50

Table 4 *Multivariate analysis of influence of variables on left ventricular function (ejection fraction)*

	Regression coefficient	*t value*	*p*
	Rest		
Cyclosporin	6·58	2·13	< 0·05
Recipient's age	−0·20	−1·71	< 0·10
Donor's age	−0·12	−0·69	< 0·50
Acute rejection	−0·66	−1·00	< 0·50
Donor's sex (M)	−3·10	−1·24	< 0·50
Ischaemia time	−0·03	−1·36	< 0·50
Recipient's sex (M)	−1·71	−0·34	> 0·50
	Exercise		
Cyclosporin	11·36	3·08	< 0·01
Recipient's age	0·01	0·01	> 0·50
Donor's age	−0·16	−0·72	< 0·50
Acute rejection	−0·31	−0·40	> 0·50
Donor's sex (M)	2·47	0·80	< 0·50
Ischaemia time	−0·03	−1·04	< 0·50
Recipient's sex (M)	0·64	0·11	> 0·50

SUBGROUP ANALYSIS

Table 5 shows an examination of factors relating to patients with the lowest (group A) and highest (group B) ejection fractions.

Analysis of results confirmed that there is no significant difference between the distribution of factors apart from the type of immunosuppression used (table 6).

IMMUNOSUPPRESSION: DISTRIBUTION OF VARIABLES

Figure 6 shows the distribution of variables in the two immunosuppression treatment groups.

Discussion

Cardiac transplantation has become an effective therapeutic option in the management of end stage heart disease and can be performed with a low operative mortality and early postoperative mortality. The success of the procedure, however, will be determined by its ability to maintain normal cardiac performance both at rest and on exercise in the long term.

In this study, we measured left ventricular ejection fraction determined by radionuclide angiography because this technique is non-invasive and provides some information about changes on exercise. These variables, however, in common with all ejection phase indices, suffer the disadvantage of being load-dependent. In a previous study we showed that after transplantation, the inotropic state of the left ventricle determined by load-independent indices was normal.[6] But this form of assessment of ventricular

Table 5 *Distribution of variables in patients with lowest ejection fractions (group A) and highest ejection fractions (group B)*

Case No	*EF%* *Rest Ex*	*Recipient's age/sex*	*Donor's age/sex*	*Acute rejection*	*Ischaemia time*	*Immuno-suppression*
Group A:						
1	32 (40)	47 M	25 M	6	110	Pred/Aza
2	39 (35)	19 F	30 M	6	190	Cya/Aza
3	40 (—)	48 M	39 F	4	150	Cya/Aza
4	41 (55)	46 M	16 M	3	115	Cya/Aza
5	42 (—)	54 M	20 F	3	255	Cya/Aza
6	43 (55)	51 M	24 M	3	115	Cya/Aza
7	44 (—)	46 M	23 F	3	90	Pred/Aza
8	45 (54)	50 M	18 M	3	128	Pred/Aza
Group B:						
1	91 (95)	36 F	22 M	3	99	Cya/Aza
2	91 (90)	43 M	32 F	0	120	Cya/Aza
3	88 (96)	14 M	9 M	3	125	Cya/Aza
4	88 (95)	53 M	35 M	5	120	Cya/Aza
5	83 (85)	44 M	18 M	1	157	Cya/Aza
6	83 (—)	34 M	36 M	0	239	Cya/Aza
7	82 (79)	44 M	26 M	5	80	Cya/Aza
8	80 (80)	48 M	19 M	4	139	Cya/Aza

Aza, azathioprine, Cya, cyclosporin; Pred, prednisolone.

function could not be applied to the large numbers of patients in the current study and therefore the two studies cannot be compared directly.

We found that in most cases the systolic function of the transplanted heart, as determined by left ventricular ejection fraction at rest and on exercise, was well maintained one year after operation. These findings accord with other studies in which radionuclide angiography was used[7, 8] and with data from cardiac catheterisation one year after transplantation.[9, 10] Contrary to the findings of Devineni *et al* who saw no increase in ejection fraction on exercise in patients treated with cyclosporin,[11] we noted a significant increase in ejection fraction on exercise (72·5(1·4)%, compared with resting values 65·6(1·2)%) in the cyclosporin treated group. These results were significantly better than for those in patients treated with conventional immunosuppression (61·1(2·5)%, 57·7(2·7)% respectively).

We found that the only factor that was significantly associated with improved left ventricular function both at rest and on exercise was treatment with cyclosporin. The cyclosporin and azathioprine patients were significantly younger (43·4 *vs* 47·3 yr) and had fewer episodes of acute rejection (2·50 *vs* 3·73) in the first year after transplantation than patients given prednisolone and azathioprine. In addition, their left ventricular function was better despite a significantly longer ischaemia time (142·5 *vs* 118·2 min) and a higher frequency of hypertension (43·6% *vs* 10·5%). These factors assessed individually were not shown to exert significant influence upon ventricular function although there was a trend for younger donor and recipient age and, to a lesser extent, shorter ischaemia time and smaller number of rejection episodes to have a favourable influence on left ventricular function. Therefore, the mechanism by which cyclosporin exerts its beneficial effect on systolic function has not been defined. Despite examination of the distribution of variables in patients with the highest and lowest ejection fractions, no factor other than the type of immunosuppression used was identified as being an important determinant of ventricular function.

This work is part of a continuing programme to evaluate the long term results of cardiac transplantation. It is hoped that the information provided will help in optimising the results of this procedure.

Table 6 *Comparison of ejection fraction (mean (SEM)) and values of variables (mean (SEM)) between group A and group B*

	EF%	*Recipient's age**	*Donor's age**	*Acute rejection**	*Ischaemia time**	*Immuno-suppression*
Group A	40·7 (1·44)	45·2 (3·80)	24·4 (2·60)	3·87 (0·48)	144·1 (19·2)	Cya/Aza 5, Pred/Aza 3
Group B	85·7 (1·51)	39·5 (4·20)	24·6 (3·37)	2·62 (0·73)	134·8 (17·0)	Cya/Aza 8, Pred/Aza 0

*There was no significant difference between groups A and B for any of these variables.

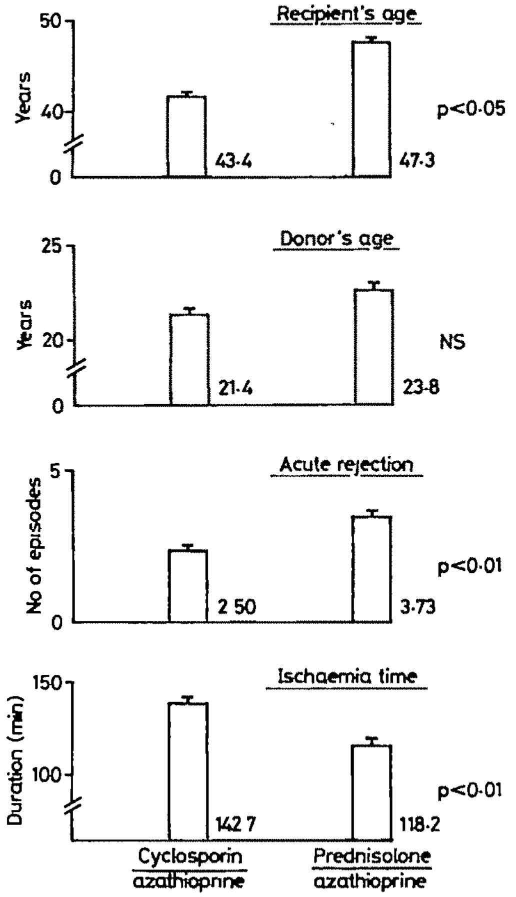

Fig 6 *Distribution of variables in groups treated with cyclosporin/azathioprine or prednisolone/azathioprine.*

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Effect of nifedipine on enzymatically estimated infarct size in the early phase of acute myocardial infarction

L J E WALKER, G MACKENZIE, A A J ADGEY

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SUMMARY In a double blind placebo controlled trial, 434 patients with suspected myocardial infarction were randomised to treatment with nifedipine (n = 217) or placebo (n = 217) within six hours from the onset of chest pain. During the treatment period of 48 hours, a 10 mg capsule containing nifedipine or placebo was given sublingually every four hours for 24 hours, then orally every four hours for the next 24 hours. Acute myocardial infarction was confirmed in 295 patients (146 in the nifedipine group and 149 in the placebo group). The median delay time to intervention with nifedipine in patients with acute myocardial infarction was 111 minutes. Infarct size was assessed by the estimation of release of creatine kinase isoenzyme MB and creatine kinase from blood samples taken every four hours for 48 hours. The total mean (SEM) creatine kinase MB released was 406·4 (27·2) IU/l in the nifedipine group and 345·7 (20·5) IU/l in the placebo group. Total mean (SEM) creatine kinase released was 2749·6 (165·1) IU/l in the nifedipine group and 2698·4 (145·9) IU/l in the placebo group. In hospital mortality was similar for both the nifedipine and placebo groups (6·6% and 5·8% respectively). Treatment with nifedipine in the early phase of acute myocardial infarction seems to have no effect on enzymatically measured infarct size.

Experiments in dogs suggest that nifedipine, a calcium channel blocking agent, can reduce the area of myocardial necrosis after coronary artery occlusion.[1–6] Nifedipine can reduce cardiac work, and therefore myocardial oxygen demand, by decreasing peripheral vascular resistance as a result of its strong peripheral vasodilatory effect. It can also increase coronary blood flow by coronary artery vasodilatation and improve collateral blood flow.[1 3 4] At a cellular level, nifedipine has been shown to reduce intramitochondrial calcium overload.[4]

The success of nifedipine as a means of reducing infarct size in dogs has not been reproduced in clinical studies. This is perhaps surprising, in view of the apparently beneficial haemodynamic effects of nifedipine in the early phase of acute myocardial infarction in man.[7] Two randomised, double blind, placebo controlled studies have failed to show evidence of reduction of myocardial infarct size[8 9] after the administration of nifedipine in patients with acute myocardial infarction. These two groups hypothesised that the relatively long delay to intervention with nifedipine in their studies (4·6 (0·1) hour (mean (SEM)) in the study by Muller *et al*,[8] 5·5 (2·9) hour (mean (SD)) in the study by Sirnes *et al*[9]) may have accounted for the failure of nifedipine to limit infarct size. A randomised double blind study of patients seen within 24 hours of the onset of symptoms of acute myocardial infarction showed no reduction in one month mortality in those who were treated actively with nifedipine compared with the placebo group.[10] We planned to minimise the delay to intervention with nifedipine by starting treatment when patients were first seen by the staff of the mobile coronary care unit.

Patients and methods

All patients admitted with suspected myocardial infarction to the Regional Medical Cardiology Centre, Royal Victoria Hospital between December 1984

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and February 1986 were considered for entry to the study, which was double blind, randomised, and placebo controlled. Verbal consent was obtained initially. The variability of infarct size as measured by total release of creatine kinase MB isoenzyme was assessed from 55 patients who entered a pilot study. From this it was estimated that 200 patients with definite myocardial infarction were needed in the double blind study to detect a 20% reduction in infarct size. Definite myocardial infarction was defined as an increase in peak creatine kinase MB to >30 IU/l (more than twice the upper limit of normal) in a patient with central chest pain for ≥ 30 minutes that appeared to be cardiac in origin regardless of electrocardiographic changes.

We excluded patients seen ≥ 6 hours after the onset of pain, those aged >75 years, and those with systolic blood pressure of ≤ 85 mm Hg.

When patients were first seen an intravenous cannula was inserted and intravenous analgesia was given if required. When the patients' condition was stable their eligibility for entry to the study was considered. Patients were randomly allocated to treatment with nifedipine or placebo by the attending doctor, who selected the next container available from a series of sequentially numbered containers provided by the pharmacy department and labelled as dictated by a randomisation schedule supplied by the statistician. Each container held sufficient capsules of either nifedipine or placebo to last the 48 hour period of treatment. Access to information on which container contained nifedipine or placebo was restricted to the hospital pharmacist and the data processing supervisor. After the patient was discharged from hospital the supervisor broke the code to record the allocation to treatment with nifedipine or placebo on the questionnaire that recorded data on each patient.

The initial sublingual dose of 10 mg nifedipine or placebo was repeated every four hours for 24 hours, and then an oral dose was given every four hours for the next 24 hours. When the patient was first seen 10 ml of venous blood was taken. Further samples were taken from a heparinised intravenous cannula every four hours throughout the 48 hour study period for later estimation of creatine kinase MB, creatine kinase, aspartate transaminase, and myoglobin.

All samples were centrifuged within 24 hours of being drawn and the sera were pipetted off and stored at 4°C. Subsequently these samples were analysed in batches. Creatine kinase and aspartate transaminase were assayed on a multichannel analyser. We used the CK-MB (NAC-act) UV-system kit (Boehringer Mannheim Diagnostica). All enzymes were assayed at 37°C. We used the Myoglobin RIA kit of NMS Pharmaceuticals for the radioimmunoassay of serum myoglobin.

Several hours after entry to the study, when the effect of any narcotic analgesia had worn off, patients were asked whether they wished to remain in the study. Pulse and blood pressure were recorded every half hour for two hours, then the pulse was measured hourly and blood pressure every four hours while the patient remained in the coronary care unit. Routine investigations (for example blood gases and electrocardiograms) took place as usual in the coronary care unit.

Intravenous streptokinase was given to 44 patients in this study (27 of whom were in the nifedipine group and 17 in the placebo group). Criteria for the administration of this drug were (*a*) age <70, (*b*) ST segment elevation of ≥ 4 mm on the initial electrocardiogram, (*c*) total delay time <4 hours, (*d*) no contraindications to anticoagulant treatment. In patients with successful recanalisation after streptokinase treatment, creatine kinase concentration peaks earlier and these patients have a greater cumulative release of creatine kinase than conventionally treated patients with an infarct of similar size.[11] For this reason patients who had received streptokinase were excluded retrospectively from the randomised controlled trial.

Patients were withdrawn from the study if (*a*) two consecutive capsules had to be omitted because systolic blood pressure had fallen to <85 mm Hg or (*b*) if the patient refused to participate further, or (*c*) if side effects developed that seemed to be related to nifedipine treatment.

One of us completed a questionnaire on all entrants to the study. This contained information on patients' baseline characteristics, cardiac enzyme results, need for additional drug treatment during the 48 hour study period, and major complications occurring during the hospital stay. The data were entered into a magnetic file on a PDP 11/34A computer by the staff of the data processing department of the Department of Community Medicine, of Queen's University, Belfast.

CALCULATION OF INFARCT SIZE

Infarct size was calculated by a computer program incorporating Norris's adaptation of Sobel's formula (that is integrated appearance function for creatine kinase $= Et + Kd \sum E\,dt$).[12] All estimates of total creatine kinase and total creatine kinase MB released using this program were made by one of us. The peak values of creatine kinase, creatine kinase MB, aspartate transaminase, and myoglobin and the time from the onset of chest pain to peak values were also recorded.

On completion of the study, statistical analyses were carried out by SPSS-11 (*Statistical Package for the Social Sciences*) on a PDP 11/34A computer. Statistical tests used included χ^2 test on discrete

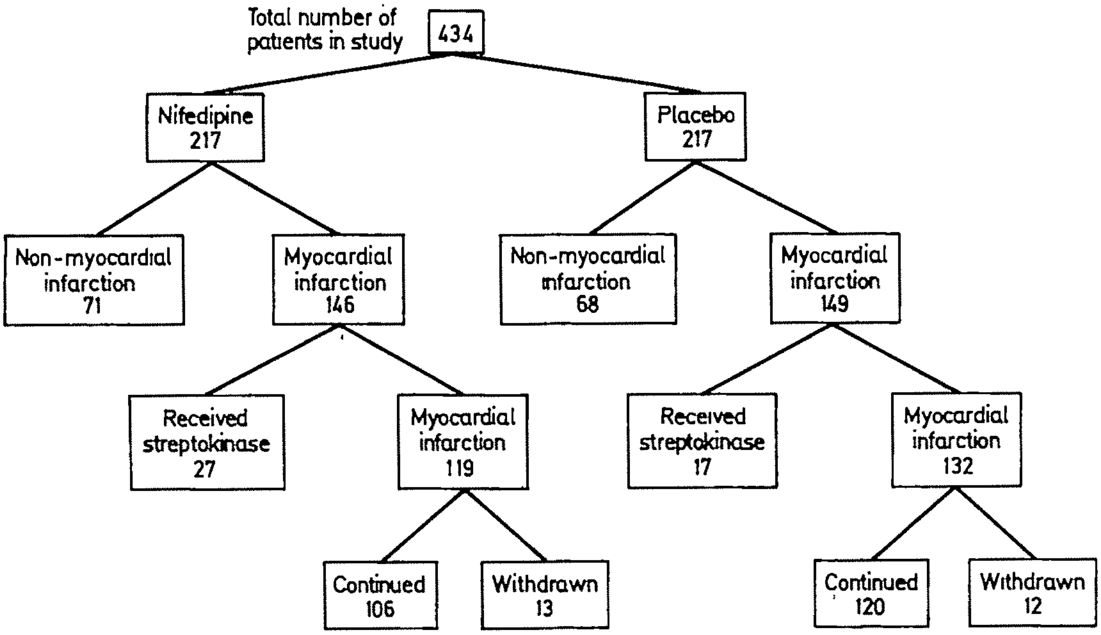

Fig 1 *Distribution of patients between nifedipine and placebo treated groups.*

variables and Student's *t* test and one way analysis of variance on continuous variables. The 5% level of significance was used throughout the study. Multiple regression methods of analysis were also used.

Results

Four hundred and thirty four patients with suspected myocardial infarction entered the study. Two hundred and seventeen were randomised to treatment with nifedipine and 217 to placebo. Acute myocardial infarction was confirmed in 295 patients—146 in the treatment group and 149 in the placebo group. Of 44 patients with definite myocardial infarction who received thrombolytic treatment, 27 were in the treatment group and 17 were in the placebo group. This difference in the proportion of patients allocated to treatment or placebo was not statistically significant. A further 25 patients withdrew from the study (13 in the treatment and 12 in the placebo group) (fig 1). Reasons for withdrawal included: (*a*) patient refusal to participate further (eight in the nifedipine treated group and five in the placebo group); (*b*) development of hypotension (systolic blood pressure <85 mm Hg) in five patients in the nifedipine treated group and six patients in the placebo group; (*c*) need for nifedipine treatment in one patient in the placebo group. Data from patients who received streptokinase or who were withdrawn from the study were excluded retrospectively from the analysis. Tables 1 and 2 summarise baseline characteristics of the remaining 226 patients with myocardial infarction who completed the study. Only three baseline characteristics were significantly different in the nifedipine and placebo groups. More patients (60: 106 (56·6%)) in the nifedipine group had a history of angina than those in the placebo group (50: 120 (41·7%)) ($p < 0·05$). A significantly smaller proportion of patients in the nifedipine group were current smokers than in the placebo group (34·9% versus 51·7% respectively) ($p < 0·05$). Patients in the nifedipine group were less likely to have needed atropine when they were first seen (2·8% versus 9·2%) ($p < 0·05$) (table 1).

CARDIAC ENZYME DATA

Values for peak creatine kinase MB, total creatine kinase MB released (figs 2 and 3), peak creatine kinase, total creatine kinase released, peak aspartate transaminase, peak myoglobin, and the times to the peak activities of all the enzymes in patients in the nifedipine and placebo groups were compared by Student's *t* test, as were the values of the individual dissociation constants (Kd) used in the estimation of enzyme release. In all but 15 patients (eight in the nifedipine group and seven patients in the placebo group) the size of the infarct could be estimated from the total creatine kinase MB released. Results were

Table 1 *Baseline variables in the 226 patients with myocardial infarction randomised to nifedipine (N) or placebo (P)*

Baseline variable	*N(%) (n=106)*	*P(%) (n=120)*
Sex (male)	87 (82·1)	95 (79·2)
Past history of:		
Angina	60 (56·6)	50 (41·7)
Hypertension	31 (29·2)	23 (19·2)
Diabetes mellitus	3 (2·8)	10 (8·3)
Dyspnoea caused by coronary disease	1 (0·9)	3 (2·5)
Previous myocardial infarction	35 (33·0)	37 (30·8)
Current smoker	37 (34·9)	62 (51·7)
Regular medication before entry to the study:		
Nifedipine	25 (23·6)	23 (19·2)
β blocker	26 (24·5)	25 (20·8)
Diuretic	23 (21·7)	23 (19·2)
Long acting nitrate	10 (9·4)	16 (13·3)
Resuscitation from VF before entry to study	4 (3·8)	4 (3·3)
Medication before being seen by ward staff:		
Narcotic analgesia	28 (26·4)	21 (17·5)
Sublingual glyceryl trinitrate	27 (25·5)	25 (20·8)
Cardioactive drugs from ward staff:		
β blocker	4 (3·8)	5 (4·2)
Diuretic	14 (13·2)	16 (13·3)
Atropine	3 (2·8)	11 (9·2)
Electrocardiographic data:		
Initial heart rhythm sinus	105 (99·1)	117 (97·5)
ST segment elevation on the initial ECG	62 (58·5)	79 (65·8)
Site of infarct:		
Anterior	43 (40·6)	51 (42·5)
Inferior	38 (35·8)	41 (34·2)
Other	25 (23·5)	28 (23·3)
Type of infarct:		
Transmural	69 (65·1)	76 (63·3)
Subendocardial	14 (13·2)	20 (16·7)
Other	23 (21·7)	24 (20·0)
No conduction disturbance on the initial ECG	101 (95·3)	115 (95·8)
Initial chest *x* ray:		
Normal	70 (66·0)	78 (65·0)
Pulmonary vascular congestion	28 (26·4)	34 (28·3)
Pulmonary oedema	8 (7·5)	8 (6·7)

ECG, electrocardiogram; VF, ventricular fibrillation.

not available in these patients, either because a series of blood samples was incomplete or because fluctuation of enzyme activity made enzymatic estimation of infarct size impossible. In two patients in the treatment group and one patient in the placebo group, peak creatine kinase MB could be identified even though estimation of total creatine kinase MB released was not feasible.

Total creatine kinase MB released was 406·43 (27·22) IU/l (mean (SEM)) in patients in the treatment group (n = 98) and 345·75 (20·48) IU/l in patients in the placebo group (n = 113) (table 3). This difference was not statistically significant. The range of total creatine kinase MB released was 51–1470 IU/l in the treatment group and 37–1199 IU/l in the placebo group (table 3, fig 2). Peak creatine kinase MB was not significantly different in the treatment group (n = 100) and in the placebo group (n = 114) (211·91 (12·77) and 189·38 (9·73) IU/l respectively). The range of values for peak creatine kinase MB was 45–613 IU/l in the treatment group and 36–526 IU/l in the placebo group (fig 3).

Table 2 *Comparison of the means (SEM) of the continuous variables in the 226 patients with myocardial infarction*

	Nifedipine (n=106)	*Placebo (n=120)*	*t*
Age (yr)	60·10 (0·85)	58·63 (0·89)	1·16
Weight (kg)	73·78 (1·26)	73·83 (1·04)	0·03
Delay time (min)	140·16 (8·02)	141·46 (7·43)	0·12
Median delay time (min)	110·67	128·50	
Initial serum potassium* (mmol/l)	4·13 (0·52)	4·04 (0·45)	1·36
Initial urea (mmol/l)	6·18 (0·23)	6·14 (0·18)	0·13
Initial heart rate (beats/min)	77·68 (1·37)	79·49 (1·46)	0·92
Initial systolic blood pressure (mm Hg)	133·11 (2·40)	134·19 (2·28)	0·33

Multiple regression analysis showed no evidence of a relation between the three baseline factors known to differ between treatment and placebo groups and in peak creatine kinase MB or total creatine kinase MB released.

Estimates of infarct size from creatine kinase were available in fewer patients than estimates from the creatine kinase MB isoenzyme, primarily because creatine kinase activity had sometimes not returned to baseline values by the end of our 48 hour sampling period. This was the case in 10 (9·4%) patients in the treatment group and seven (5·8%) patients in the placebo group. In addition, we excluded results from patients in whom cardioversion was performed or in whom cardiogenic shock had developed or who received intramuscular injections, because these factors are known to interfere with creatine kinase activity. Total creatine kinase released was 2749·64 (165·14) IU/l in the treatment group (n = 77), and 2698·39 (145·86) IU/l in the placebo group (n = 89) (table 4). The range of total creatine kinase released was 591–9623 IU/l in the treatment group and 483–7154 IU/l in the placebo group (table 4). Peak creatine kinase was 1938·24 (156·63) IU/l in the treatment group (n = 87), and 1839·58 (118·64) IU/l

Table 3 *Total creatine kinase MB (IU/l) released by nifedipine and placebo treated groups*

	Nifedipine (n=98) (Mean (SEM))	*Placebo (n=113) (Mean (SEM))*
Total creatine kinase MB released	406·43 (27·22)	345·75 (20·48)
Range of total creatine kinase MB	51–1470	37–1199

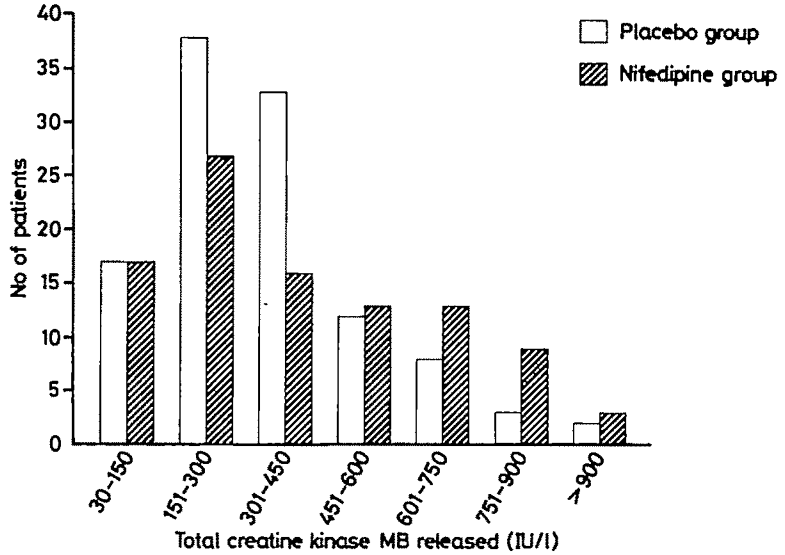

Fig 2 *Total creatine kinase MB released by patients with myocardial infarction, 98 of whom were treated with nifedipine and 113 of whom were treated with placebo.*

in the placebo group (n = 96). The range of peak creatine kinase values was 423–9748 IU/l in the treatment group and 409–7923 IU/l in the placebo group. None of these differences was statistically significant.

The time from the onset of pain to the peak creatine kinase MB was 18·20 (0·54) hours in the treatment group and 17·98 (0·58) hours in the placebo group. The time from the onset of pain to peak creatine kinase activity was 21·67 (0·70) hours in the treatment group and 21·34 (0·66) hours in the placebo group. Neither of these differences was statistically significant.

Kd VALUES

The mean (SEM) value of Kd used to estimate infarct size from creatine kinase MB in patients in the nifedipine group was 10772 (379) (10^{-7}) and 10252 (308) (10^{-7}) in the placebo group. The mean (SEM) value of Kd used to estimate infarct size from creatine kinase in patients in the nifedipine group was 7536

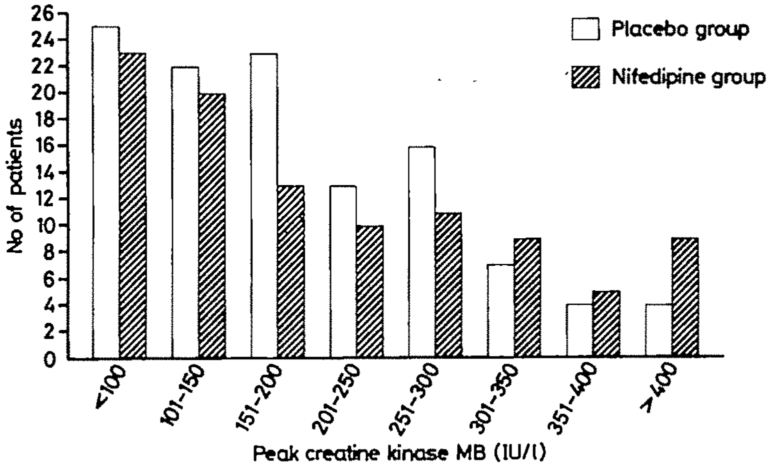

Fig 3 *Distribution of the peak creatine kinase MB values in 100 patients with myocardial infarction treated with nifedipine and 114 treated with placebo.*

Table 4 *Total creatine kinase (IU/l) released by nifedipine and placebo treated groups*

	Nifedipine (n = 77) (Mean (SEM))	*Placebo (n = 89) (Mean (SEM))*
Total creatine kinase released	2749·64 (165·14)	2698·39 (145·86)
Range of creatine kinase	591–9623	483–7154

(291) (10^{-7}) and 7042 (277) (10^{-7}) in the placebo group. These values were not significantly different (Student's *t* test).

ASPARTATE TRANSAMINASE AND MYOGLOBIN

Patients were excluded from the analysis if cardioversion had been performed, if cardiogenic shock had developed, or if they had had intramuscular injections, because these factors are known to interfere with measurement of aspartate transaminase and myoglobin.

Peak mean (SEM) aspartate transaminase was 271·34 (17·36) IU/l in the treatment group and 268·51 (16·32) IU/l in the placebo group. The range of peak aspartate transaminase was 58–840 IU/l in the treatment group and 39–930 IU/l in the placebo group. Peak mean (SEM) myoglobin was 1029 (108·34) IU/l in the treatment group and 886·36 (72·88) IU/l in the placebo group. The range of peak myoglobin was 54–7125 IU/l in the treatment group and 53–4725 IU/l in the placebo group.

Mean (SEM) time to peak aspartate transaminase was 24·35 (0·66) hours in the treatment group and 23·79 (0·65) hours in the placebo group. Time to peak myoglobin was 10·99 (0·47) hours in the treatment group and 9·63 (0·45) hours in the placebo group.

Thus none of the measured variables was significantly different in the nifedipine and placebo groups.

The frequency of early ventricular fibrillation during the 48 hour study period, and of pulmonary oedema, reinfarction, and cardiogenic shock during the hospital stay was not different in the two groups (table 5). The need for special procedures, including cardioversion and insertion of a temporary transvenous pacemaker, was not significantly different in the two groups (χ^2 test) (table 5). Seven patients in each group died during the hospital stay (table 5).

Table 5 *Occurrence of early ventricular fibrillation during the 48 hour study period and in hospital complications with need for special procedures in patients with myocardial infarction*

	Nifedipine (%) (n = 106)	*Placebo (%) (n = 120)*
Early ventricular fibrillation	4 (3·8)	9 (7·5)
Pulmonary oedema	12 (11·3)	16 (13·3)
Reinfarction	5 (4·7)	3 (2·5)
Cardiogenic shock	3 (2·8)	1 (0·8)
Cardioversion	10 (9·4)	12 (10·0)
Temporary pacemaker insertion	6 (5·7)	2 (1·7)
In hospital mortality	7 (6·6)	7 (5·8)

Table 6 *Need for additional treatment during the 48 hour study period in patients with myocardial infarction*

Additional drug	*Nifedipine (%) (n = 106)*	*Placebo (%) (n = 120)*
Metoclopramide	18 (17·0)	21 (17·5)
β blocker	39 (36·8)	37 (30·8)
Diuretic	48 (45·3)	58 (48·3)
Digoxin	8 (7·5)	8 (9·7)
Lignocaine	16 (15·1)	21 (17·5)
Mexiletine	9 (8·5)	13 (10·8)
Long acting nitrate	37 (34·9)	53 (44·2)
Dobutamine	5 (4·7)	2 (1·7)

The needs of patients for additional drugs (metoclopramide, β blockers, diuretics, digoxin, lignocaine or mexiletine, and preparations containing nitrate or dobutamine) in the 48 hour study period were not significantly different in the two groups (table 6).

SUBGROUP ANALYSIS

Infarct sizes estimated by total creatine kinase MB released by different sites and types of myocardial infarction were compared. The number of patients was too small for meaningful analysis, except in patients with transmural myocardial infarction. In these patients, total mean (SEM) creatine kinase MB released was significantly larger (496·4 (32·0) IU/l) in the treatment group (n = 65), than in the placebo group (383·9 (24·4) IU/l) (n = 72).

Discussion

The 48 hour treatment regimen of nifedipine used in this study did not affect infarct size as measured by total creatine kinase MB released or total creatine kinase released. Nor did it have an effect on cruder indicators of infarct size, including peak activities of creatine kinase MB, peak creatine kinase, peak aspartate transaminase, and peak myoglobin concentration. These findings confirm the results of similarly designed studies by Muller *et al*[8] and Sirnes *et al*,[9] who suspected that the failure of nifedipine to limit infarct size was related to the relatively late intervention times in their studies (mean delay 4·6 hours and 5·5 hours respectively). This was not a feature of our study (mean total delay time in the treatment group was 2·3 hours). In a study by Branagan *et al* (1986) mean delay time to intervention with nifedipine was

3·3 hours but the number of patients in this study in whom infarct size was obtainable was too small for meaningful analysis (23 in the nifedipine treated group and 17 in the placebo group) and there was no difference between the groups reported.[13] Perhaps the dose and frequency of nifedipine used were suboptimal. But we were reluctant to expose patients to the hazard of excessive vasodilatation which could have resulted with larger doses of nifedipine. The dose of nifedipine chosen had in any case been shown to produce favourable haemodynamic effects in acute myocardial infarction.[7] This earlier study found that in patients treated with nifedipine cardiac output was significantly higher and peripheral vascular resistance significantly lower than in control patients. Logically this reduction in afterload should reduce myocardial oxygen demand because cardiac work is less and hence infarct size should be reduced.

WHY DOES NIFEDIPINE FAIL TO LIMIT INFARCT SIZE?

The apparent lack of effect of nifedipine on the limitation of infarct size may be related to the development of relative hypotension in some patients, which would offset any benefit. Such a phenomenon was seen in experimental studies by Selwyn *et al*[3] and Welman *et al.*[2] They found that infarct size was increased in subgroups of animals treated with a dose of nifedipine that was 13 times higher than the dose that reduced infarct size. They suggested that this result could have been caused by the relative hypotension and reflex tachycardia produced by the larger dose of nifedipine. There was no evidence to suggest that this occurred in the studies performed by Muller *et al*[8] and Sirnes *et al.*[9] Similarly, in our study there was nothing to suggest that relative hypotension was a problem—there was no significant difference in the number of patients with cardiogenic shock between the nifedipine treated group and the placebo group (table 5). Perhaps the lack of evidence of a reduction in infarct size was related to the enzymatic method used. None the less, enzymatic estimation of infarct size by release of total creatine kinase MB has been validated by Grande *et al*[14] and Hackel *et al*[15] who found a close correlation with anatomical infarct size.

Our finding of a significant increase in infarct size as estimated by total creatine kinase MB released in patients with transmural infarction in the nifedipine treated group was unexpected and is difficult to explain.

Any intervention study in which enzymatic estimation of infarct size is the major end point requires a large number of patients in the treatment and control groups to allow for the variability of infarct size between patients. It is possible that nifedipine may have decreased infarct size but not to a detectable extent, given the statistical power of our study, which was designed to have a 95% chance of detecting a 20% reduction in infarct size as measured by total creatine kinase MB released. Estimation of the numbers required for any intervention study in acute myocardial infarction is complicated by the fact that the scale of reduction necessary to affect prognosis is not known. Like us, most investigators have aimed at discovering whether a 20 or 30% reduction in infarct size could be obtained. What is known, however, is that in patients with myocardial infarction who have cardiogenic shock there is invariably evidence of extensive myocardial damage.[16–18]

In conclusion, early intervention with nifedipine treatment in the acute phase of myocardial infarction appears to have no effect on infarct size as measured enzymatically by total creatine kinase MB released, total creatine kinase released, nor does it seem to have any impact on peak aspartate transaminase activity or peak myoglobin concentrations. In hospital mortality in treatment and placebo groups was not significantly different. The contrast in the efficacy of nifedipine in the experimental and clinical settings makes us doubt the value of experimental assessment of limitation of infarct size.

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Nifedipine in acute myocardial infarction: an assessment of left ventricular function, infarct size, and infarct expansion
A double blind, randomised, placebo controlled trial

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SUMMARY The influence of nifedipine on left ventricular ejection fraction, infarct size, and infarct expansion was studied in a prospective, double blind, randomised, placebo controlled trial in 132 patients with low risk acute myocardial infarction of < 12 hours duration, defined by an initial left ventricular ejection fraction >35% and clinical Killip class of ≤II. Sixty four patients were assigned to nifedipine 120 mg/day and 68 to placebo. Treatment was started on average (SEM) 8·0 (0·2) hours after onset of pain and continued for six weeks. Gated blood pool scans, thallium scans, and cross sectional echocardiograms were performed before treatment and at 10 days. There were no significant differences between the two groups in age, sex, cardiac risk factors, or use of other medications. Mean (SEM) global left ventricular ejection fraction was not different before treatment (nifedipine group 53 (2%), placebo group 55 (2%) and did not differ at 10 days (nifedipine group 54 (2%), placebo group 52 (2%). There were also no differences in regional wall motion or regional ejection fractions. Thallium defects quantified by computer analysis were similar in both groups before treatment (nifedipine 7·8 (0·7), placebo 7·9 (0·7)) and at 10 days (nifedipine 5·3 (0·7) placebo 5·3 (0·7)). In the subgroup of patients with transmural infarction who had good quality echocardiograms and serial studies (n = 30), there was no difference in mean (SEM) baseline infarct segment lengths between the two groups (nifedipine 70 (4) mm, placebo 65 (4) mm); however, the nifedipine group demonstrated no significant change in infarct segment length between the initial and 10 day studies (+0·6 (3) mm) while there was a significant increase in the infarct segment length in the placebo group (+7·8 (4) mm). The infarct segment length increased by ≥1 cm in seven (47%) placebo patients but in only one (7%) nifedipine patient. The nifedipine group had a significant initial 10% decrease in mean arterial pressure whereas there was no change in the placebo group; this blood pressure difference persisted for 10 days.

Thus although the early administration of nifedipine has no detectable effect on clinical outcome and infarction size, it may reduce early infarct expansion via an afterload reduction mechanism in patients with transmural infarction. These initial results must be interpreted with caution and need to be confirmed in a larger trial.

Nifedipine is a potent dihydropyridine calcium antagonist which inhibits the calcium dependent excitation-contraction coupling processes in cardiac and smooth vascular muscle.[1-3] Its efficacy is well documented in patients with stable[4 5] and unstable

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angina,[6-8] and there are theoretical reasons to suggest that it may also be beneficial in the treatment of acute myocardial infarction. These include a reduction of afterload mediated by peripheral vasodilatation, an increase in coronary flow via coronary vasodilator and antispasm effects, and the possibility of a direct protective effect on the myocardium. Animal studies have shown a reduction of infarct size with nifedipine given before and after coronary occlusion.[9-11] In addition, nifedipine may limit infarct expansion because left ventricular wall tension is an important determinant of expansion when the infarction is transmural.[12-14]

Several controlled studies have examined the effect of the early administration of nifedipine in patients with acute myocardial infarction and have demonstrated no significant reduction in myocardial infarction size measured by creatine kinase release.[15-17] One of these studies suggested that there may be an increased early mortality associated with nifedipine treatment[15]; however, the TRENT study which randomised 4491 patients showed no significant effect of lower dose nifedipine treatment (10 mg four times daily) on mortality.[17] None of these studies has shown beneficial effects of early nifedipine treatment on indices of infarction size or clinical outcome. The present study examines the effects of the early administration of a larger dose of nifedipine on global and regional left ventricular function, infarct size by quantitative scintigraphic techniques, and infarct expansion in patients with acute myocardial infarction.

Patients and methods

PATIENT SELECTION

We studied patients admitted to the coronary care units at the Johns Hopkins Hospital and Francis Scott Key Medical Center between the ages of 30 and 75 years with the clinical diagnosis of acute myocardial infarction of less than 12 hours duration. We selected only "low risk" Killip class I or II patients with an initial left ventricular ejection fraction by gated blood pool scan of > 35%. Myocardial infarction was defined as typical ischaemic chest pain which lasted for at least 30 minutes with associated electrocardiographic changes of ST segment elevation > 1 mm, new Q waves, or persistent T wave inversions in at least two leads. Enrolment did not require enzymatic confirmation of infarction because treatment had to be started within 12 hours of the onset of chest pain. Informed written consent, which had been approved by the hospitals' joint committee on clinical investigation, was obtained. Patients were excluded if they had a systolic pressure of < 100 mm Hg, symptomatic cerebrovascular disease, P-R interval > 0·24 s, or higher degree atrioventricular block without a pacemaker in place, pulmonary oedema, cardiogenic shock, or if they were taking a calcium antagonist at the time of hospital admission.

STUDY DESIGN

After the patient had given informed consent to one of the study investigators, baseline thallium and gated blood pool scans were obtained in the coronary care unit with a portable gammacamera. These studies were performed by a 24 hour on-call team of experienced research nuclear cardiology technicians and were completed within 1·5–2 hours. After completion of the initial scans, the patients received, in a randomised double blind fashion, one capsule of the study drug, which was either nifedipine 10 mg or a placebo capsule of identical appearance. Blood pressure was monitored every 10 minutes for one hour by a research nurse, and if the mean arterial pressure fell by < 10% and the systolic blood pressure was > 100 mm Hg a second study drug capsule was given. The pressure was similarly monitored for the next hour, and if the mean arterial pressure fell by < 10% and the systolic blood pressure remained > 100 mm Hg a third capsule was administered with an additional hour of monitoring. Thus a maximum maintenance study drug dose of 10–30 mg was established in each patient and this was then given every six hours for six weeks unless hypotension or any other side effect was noted.

Repeat gated blood pool scanning was performed immediately after the determination of the maintenance study drug dose and again at 10 days. Cross sectional echocardiograms were obtained within 24 hours of admission and again at 10 days in those patients who had technically interpretable initial echocardiographic studies. Twelve lead electrocardiograms were obtained daily while the patients were in the coronary care unit, and creatine kinase isoenzyme concentrations were measured every four hours for the first two days.

Routine coronary care unit management included oxygen by nasal cannula, intravenous lignocaine infusion for 24–48 hours (20–40 μg/kg/min), and full heparinisation (3000 unit bolus followed by 800–1000 U/h infusion). Nitrates and β blockers were not administered unless a patient experienced post-infarction ischaemic symptoms or if the patient was already on β blockade. Other medications including morphine sulphate, digoxin, diuretics, oral anti-arrhythmic agents, and sedatives were administered as needed.

GATED BLOOD POOL AND THALLIUM SCANNING

Thallium scans were performed in the anterior, left anterior oblique 40°, left anterior oblique 60°, and lateral projections using thallium-201, 1·5–2·0 mCi. Images were obtained with a Technicare 420 mobile gammacamera interfaced to a VIP or Medical Data Systems computer. Thallium perfusion defects were measured by an objective thallium circumferential profile technique.[18] Gated blood pool scans were performed in the anterior, left anterior oblique 40°, and lateral projections with red blood cells labelled in vivo with 25–30 mCi technetium-99m with the same mobile camera. Global and regional ejection fractions were calculated by standard Medical Data Systems programs. The left ventricular volumes, stroke volume, and cardiac outputs were calculated by a count-based method developed at the Johns Hopkins Hospital.[19] The gated blood pool images were separated into infarct and non-infarct zones by electrocardiographic correlation and by the assessment of regional wall motion abnormalities. A regional ejection fraction was then calculated for each zone from the mean of the adjacent 22·5° pre-shaped sectors overlying the left ventricle, excluding the upper medial quadrant. Once they had been defined on the initial study, the same sectors were used to calculate regional ejection fractions for infarct and non-infarct zones on serial studies. The gated blood pool and thallium scans were interpreted blindly without knowledge of the study assignment.

CROSS SECTIONAL ECHOCARDIOGRAPHY

Serial cross sectional echocardiography was performed on days 1 and 10. Particular attention was given to obtaining a good cross sectional view at the level of the papillary muscles. The serial studies were quantitatively analysed blindly by a trained technician and then reviewed blindly by an investigator (JLW). Endocardial anterior and posterior segment lengths from cross sectional end diastolic frames at the level of the papillary muscles were measured in triplicate with a computer-aided contouring system and averaged by previously published methods.[13] The anterior and posterior segment lengths were measured with the papillary muscles as landmarks,[13] and the infarct segment was identified by electrocardiographic correlation. The intraobserver variability of this technique in our laboratory was $<5\%$.[13] Because infarct expansion occurs only with transmural infarction,[12–14] only patients with transmural infarction were included in the expansion analysis.

OUTCOME VARIABLES

The primary outcome variables for this study were global and regional left ventricular function, infarct size, and echocardiographic infarct expansion on the initial and 10 day studies. The clinical outcomes of death, recurrent infarction defined as chest pain lasting longer than 30 minutes with new electrocardiographic changes and re-elevation of creatine kinase concentrations to greater than twice normal, recurrent ischaemia, and the need for coronary artery bypass surgery to control ischaemic symptoms were also examined, although the study population was not large enough to detect even large mortality differences. The calculated sample size of this study was sufficient to detect an approximate 50% difference in combined clinical outcomes (death, recurrent infarction, bypass surgery for recurrent angina symptoms) with a power of 0·7.

DATA ANALYSIS

Continuous variables were analysed by paired and non-paired t tests as appropriate. Categorical data were examined by contingency-table analysis by the χ^2 test. The proportion of patients in each study arm who experienced individual and combined clinical outcomes and the time-dependence of these outcomes were analysed by Kaplan-Meier actuarial curves, which were compared by a log-rank test with a two-tailed significance level.[20] Repeated measures analysis of variance was used to compare the blood pressures in the two groups over time. The gated blood pool scan, thallium scan, and echocardiographic data were interpreted blindly without knowledge of study drug assignment or clinical course. Data are presented as mean (SE). The analyses include all patients originally assigned to each treatment arm, according to the intention to treat principle.

Results

A total of 132 patients were randomised: 64 were assigned to nifedipine and 68 to placebo. Table 1 shows the clinical characteristics of the study population. The patients were 33 to 75 years old and 67% were men. The mean time from the onset of chest pain to the start of treatment with the study drug was 8·0 (0·2) hours for all patients. There were no significant baseline differences in the distribution of cardiovascular risk factors including previous myocardial infarction, treatment with other anti-ischaemic agents, initial Killip class, location of myocardial infarction, presence of non-transmural or transmural infarctions, size of the initial thallium defect, or initial left ventricular ejection fraction by gated blood pool scan performed before treatment.

HAEMODYNAMIC RESPONSE TO STUDY DRUG

The figure shows the mean arterial blood pressure response to the first maintenance study drug dose after completion of dose titration. The mean dose of nifedipine in the group randomised to nifedipine was 105 mg/day: 39 patients received 120 mg/day, 19

Table 1 *Comparison of baseline characteristics of patients in the nifedipine and placebo study groups**

Characteristics	*Nifedipine (n = 64)*	*Placebo (n = 68)*
Sex (male/female) (n)	45/19	44/24
Diabetes mellitus (n)	8	12
Current smoking (n)	43	48
Hypertension (n)	32	39
Previous MI (n)	14	10
Previous angina (n)	37	35
Killip class (n): O–I	43	47
II	21	21
No MI (n)	6	7
Anterior/inferoposterior MI (n)	24/34	18/43
Transmural/non-transmural MI (n)	39/19	47/14
Nitrates (oral or topical) (n)	34	32
β blockers (n)	25	24
Digoxin (n)	8	6
Antiplatelet agents (n)	5	8
Oral antiarrhythmic agents (n)	4	5
Age (years) (mean (SEM))	58 (1)	57 (1·2)
Onset of pain to treatment (mean (SEM))	8·3 (0·2)	7·7 (0·2)
Baseline LVEF (%) (mean (SEM))	53 (2)	55 (2)
Baseline thallium score (mean (SEM))	7·8 (0·7)	7·9 (0·7)

*There is no significant difference between the two groups for any characteristic listed. MI, myocardial infarction, LVEF, left ventricular ejection fraction. Computer units for thallium defect score.

received 80 mg/day, and six patients received 40 mg/day. The initial mean arterial pressures before treatment with the study drug did not differ (nifedipine 100 (2), placebo 102 (2) mm Hg) (NS). After the study drug had been given to patients the mean arterial pressure decreased by 10% in the nifedipine group with a peak effect noted at 40 minutes, while the placebo group demonstrated no significant change ($p < 0·001$ for difference between two groups). There was a minimal initial increase in the heart rate (mean of 3·0 beats per minute) in the nifedipine group, while the placebo group showed no significant change.

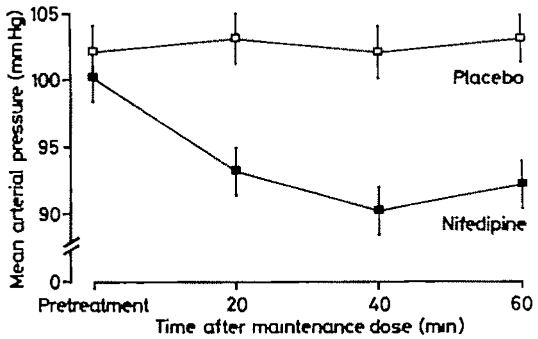

Figure *The response of the mean arterial pressure to the maintenance dose of study drug. The mean arterial pressure decreased by 10% in the nifedipine group with a peak effect noted at 40 minutes, whereas there was no significant change in the placebo group ($p < 0·001$ for difference between the two groups). Data are mean (SEM).*

CLINICAL OUTCOMES

Table 2 shows the clinical outcomes over the six week study period. Eight patients (four nifedipine, four placebo) were withdrawn from the study because of side effects. The side effects in the nifedipine group were hypotension in three and dizziness in one patient. One placebo patient was withdrawn because of hypotension and three because of dizziness and other non-specific complaints attributed to the study drug. Two other patients assigned to nifedipine and four assigned to placebo withdrew themselves prematurely from the study. The analyses of the clinical outcomes include all patients who were originally assigned to each treatment arm. Six nifedipine and seven placebo patients demonstrated no subsequent enzymatic evidence of myocardial infarction but were included in the analyses. There was no difference in the peak creatine kinase concentrations between the nifedipine (1383 (150) IU) and the placebo (1626 (152)) groups. Four patients in each treatment arm died within six weeks (6% overall mortality), and six nifedipine and seven placebo patients experienced recurrent myocardial infarction. Five nifedipine and two placebo patients underwent coronary artery bypass surgery within six weeks for persistent post-infarction angina. Thus 23% of the nifedipine patients and 19% of the placebo patients experienced either death, reinfarction, or bypass surgery for symptoms at six weeks, and there was no significant group difference for the cumulative time dependent probability of experiencing any of these outcomes (Kaplan-Meier analysis). In order to detect a statistically significant difference of this magnitude with an alpha level of 0·05 and a power of 0·8 over 1400 patients would be required in each arm of the study.

LEFT VENTRICULAR FUNCTION

Table 3 shows the global and regional left ventricular function data. There is no significant difference in baseline global ejection fractions between the nifedipine (53 (2)%) and placebo (55 (2)%) groups. There are also no differences in the immediate post-

Table 2 *Clinical outcomes during six week study period: comparison of nifedipine and placebo groups**

	Nifedipine (n = 64)	*Placebo (n = 68)*
Death	4	4
Recurrent infarction	6	7
Bypass surgery for symptoms	5	2
Side effects requiring withdrawal from study	4	4
Study withdrawals because of non-compliance	2	4

*There is no significant difference between the two groups for any of the variables listed treatment (nifedipine 54 (2)%, placebo 54 (2)%) or 10 day (nifedipine 54 (2)%, placebo 52 (2)%) studies. The present sample size is sufficient to detect a 10% difference (that is between a 50% and a 55% ejection fraction) in the mean ejection fraction between the two study groups with an alpha level of 0·05 and power of 0·7. When analysed as paired data, neither group showed a statistically significant change in ejection fraction between the initial and 10 day scans. Since patients with low initial ejection fractions tend to show improvement with time while those with high initial values tend to demonstrate a reduction as the high initial sympathetic tone decreases,[21] the change in ejection fraction was also analysed separately in the subsets of nifedipine and placebo patients with an initial ejection fraction ⩽50% and in those with an initial ejection fraction of >50%. No nifedipine effect was demonstrated as there was a similar improvement over the 10 day period in patients with a low initial ejection fraction, and a similar decline in global ejection fraction in the subset with a high initial ejection fraction. In the subgroup of patients who received early treatment (<6 hours from pain onset) there is also no significant difference in 10 day global ejection fraction between the nifedipine and placebo patients. Initial and day 10 cardiac output and ventricular volumes also were not significantly different in the nifedipine and placebo groups (table 3). The pretreatment infarct zone regional ejection fractions were 33 (2)% in the nifedipine and 35 (2)% in the placebo groups (NS). The regional ejection fractions of the non-infarct zone were 61 (1·3)% in the nifedipine and 64 (1·5)% in the placebo groups (NS). At 10 days the ejection fractions of the infarct zones were significantly improved in both the nifedipine (+6 (2)%) and placebo groups (+7·5 (2)%) and there was no difference between the two groups. In contrast, the regional non-infarct zone ejection fractions were minimally reduced in both the nifedipine (−3 (1·7)%) and placebo groups (−4 (1·6)%, table 3). Thus the net change in global ejection fraction over the 10 day period is determined by opposite trends—an increase in the infarct zones and a decrease in the non-infarct zones.

Table 3 *Comparison of resting global and regional left ventricular ejection fractions and calculated cardiac volumes and cardiac outputs in nifedipine and placebo groups**

	Nifedipine (n = 64)	*Placebo (n = 68)*
Global LVEF:		
Baseline	53 (2)	55 (2)
Post drug	54 (2)	54 (2)
10 day	54 (2)	52 (2)
Regional LVEF:		
infarct zone:		
Baseline	33 (2)	35 (2)
Post drug	34 (2)	36 (2)
10 day	41 (2)	41 (2)
non-infarct zone		
Baseline	61 (1·3)	64 (1·5)
Post drug	60 (2)	60 (2)
10 day	59 (2)	60 (2)
End diastolic volume (ml)		
Baseline	155 (5)	161 (6)
Post drug	157 (6)	166 (7)
10 day	146 (5)	157 (5)
End systolic volume (ml):		
Baseline	76 (4)	74 (4)
Post drug	76 (5)	78 (5)
10 day	68 (4)	78 (4)
Cardiac output (l/min):		
Baseline	6 1 (0 3)	6·5 (0·2)
Post drug	6·1 (0 3)	6 4 (0 3)
10 day	5·5 (0·2)	5·5 (0 2)

*There is no significant difference between the two groups for any variables listed. LVEF, left ventricular ejection fraction.

THALLIUM SCINTIGRAM RESULTS

The initial and 10 day thallium perfusion images were analysed quantitatively by methods described elsewhere.[18] The initial pretreatment thallium scores in the nifedipine (7·8 (0·7) units) and placebo (7·9 (0·7) units) groups did not differ. The day 10 thallium score was lower in both groups and also did not differ significantly (nifedipine 5·3 (0·7), placebo 5·3 (0·7)). Thus quantitative analysis of myocardial infarction size by serial (at the start of the trial and 10 days later) thallium scintigraphy showed no nifedipine effect.

INFARCT EXPANSION: CROSS SECTIONAL ECHOCARDIOGRAPHIC ANALYSES

Serial cross sectional echocardiographic studies were performed on days 1 and 10 in those patients with transmural infarctions who had not reached an unfavourable outcome in the interim and in whom technically good quality images could be obtained for quantitative contouring and analysis. Of the 132 patients who were randomised, 86 had transmural infarctions and 44 of these had good quality echocardiographic studies during the first two days that were technically adequate for detailed contouring. Fourteen of these patients were unavailable for serial studies. The technical quality of the studies was judged by a technician who was unaware of the study drug assignment.

Table 4 shows the baseline clinical characteristics of the 30 patients in the echocardiographic subset. Fifteen patients were assigned to nifedipine and 15 to placebo. There is no significant difference between the two groups with regard to age, sex, location of infarction, other medications, baseline ejection fraction, thallium score, and systolic blood pressure. There is also no significant difference in the initial infarct segment lengths between the nifedipine (70 (4) mm) and placebo (65 (4) mm) groups. None the

Table 4 *Baseline characteristics of subset of patients with transmural infarctions and serial echocardiographic studies: comparison of patients in the nifedipine and placebo groups*

Characteristics	*Nifedipine (n = 15)*	*Placebo (n = 15)*
Sex (male/female) (n)	11/4	6/9
Diabetes mellitus (n)	1	1
Current smoking* (n)	14	8
Previous angina (n)	3	8
Medications (n):		
Nitrates	3	7
β blockers	4	6
Antiplatelet agents	2	2
Initial Killip class		
I	15	12
II	0	3
Anterior/inferoposterior MI	2/13	4/11
Age (years) (mean (SEM))	55 (3)	59 (1)
Time from onset of chest pain to treatment (h) (mean (SEM))	6·9 (0·5)	7·6 (0·6)
Initial LVEF (mean (SEM))	54 (4)	56 (3)
Initial infarct segment (mm) (mean (SEM))	70 (4)	65 (4)

*(p < 0·05). There is no significant difference between the groups for any other characteristic listed. MI, myocardial infarction; LVEF, left ventricular ejection fraction.

less, there was a significant increase in infarct segment length (+7·8 (4) mm, p < 0·05) in the placebo group between the studies on day 1 and on day 10, and none in the nifedipine group (+0·6 (3) mm, p = NS). The infarct segment length increased by ≥1 cm in seven patients assigned to placebo but in only one assigned to nifedipine (p < 0·05). Both groups showed a similar increase in the non-infarct segment lengths (nifedipine 9 (4) mm, placebo 8 (4) mm, p = NS). As in the overall study population, the nifedipine group in this echocardiographic analysis showed a significant fall in systolic blood pressure 40 minutes after receiving the initial maintenance dose of the study drug (−8·1 (1) mm Hg, p = 0·04), while the placebo group did not. This difference between the groups persisted over 10 days (p < 0·05 by repeated measures analysis), and the 10 day mean arterial pressures were 81 (1) mm Hg in the nifedipine group and 87·3 (1) mm Hg in the placebo group (p = 0·02). The cardiac volumes measured by gated blood pool scans in this subgroup were not significantly different in the two treatment groups. The non-infarct segment lengths increased similarly in both groups and this may have masked differences caused by changes in infarct segments.

Discussion

The present study shows that nifedipine given to patients with acute myocardial infarction within 12 hours of the onset of pain has no detectable effect on global or regional left ventricular function or myocardial infarct size by thallium scintigraphy. The power of this individual study to detect a significant difference in mortality and reinfarction is quite low, but the present findings are consistent with other published reports of early nifedipine treatment in acute infarction.[15-17] The echocardiographic findings in a subset of patients with transmural infarction, however, suggest that early nifedipine treatment in a dose sufficient to lower mean arterial blood pressure by approximately 10% may decrease the occurrence and extent of infarct zone expansion. The clinical significance of this observation is unclear, however, and these data must be interpreted with caution as they apply to a relatively small and selected subset of the study population.

Theoretical considerations and studies in animal models suggesting that calcium antagonist treatment may limit infarct size have prompted considerable interest in the role of these agents in patients with an acute myocardial infarction.[15-17] These drugs reverse coronary vasoconstriction, which may accompany an infarction[22] and may be the proximate cause of coronary artery occlusion in some patient subsets.[23] They may also improve myocardial oxygen supply and decrease oxygen demand by increasing collateral flow and decreasing afterload via their vasodilatory effects on the coronary and peripheral circulation.[24] Although treatment with calcium antagonists reduced infarct size in some animal studies,[9-11] the effect was studied only when the agent was given before or within one hour of the onset of ischaemia. In addition, the effect may be dependent on a collateral network capable of delivering the agent to the ischaemic area itself since the benefit in dogs, which have well developed collaterals, is considerably greater than that in baboons,[25] which do not.

There have been four other randomised controlled studies examining the effect of nifedipine in patients with threatened or actual acute infarction.[15-17 26] These have focused on the enzymatic determination of infarct size and on the clinical course. A Norwegian trial showed no significant difference in creatine kinase release in the nifedipine and placebo groups.[16] Another study also reported no significant difference in infarct size estimated by creatine kinase release, but reported a higher two week mortality in the nifedipine treatment group that was not present at six months.[15] These trials were also too small to detect differences in major clinical outcomes such as mortality; however, the largest trial of nifedipine in suspected or confirmed acute infarction (the TRENT study) found that a daily dose of 40 mg of nifedipine had no significant effect on one month mortality in 4491 randomised patients.[17]

The lack of a reduction in infarct size or of a significant difference in major clinical outcomes in all of these trials may be related to several factors.

Although nifedipine is a potent coronary vasodilator, coronary vasoconstriction may have a relatively small role in most infarct patients. Even if spasm is an important initiating event, the superimposition of thrombus may prevent reperfusion with antispasm treatment alone.[27] In addition, any direct protective effect is dependent on the extent of collateral supply to the infarcted region, which is usually limited in patients with initial transmural infarctions.[28] Finally, reperfusion studies have indicated that strategies designed to salvage myocardium must be started immediately after the onset of ischaemia.[29-31] The mean time from the development of chest pain to treatment in these trials ranged from 4·6 to 8 hours, which is probably too long to achieve significant myocardial salvage.

These negative results with calcium antagonist treatment in non-selected acute infarction patients (most of whom had completed Q wave infarctions) contrast with other data supporting the efficacy of anti-ischaemic drugs for selected subsets of high risk patients in whom the potential for recurrent ischaemia after infarction is increased. The beneficial effect of calcium antagonist treatment in reducing early reinfarctions in patients with non-Q-wave infarctions,[32] the benefit of nifedipine for patients with post-infarction angina,[8 33] and the reduction of cardiac mortality by β blockers, most notably in high risk subgroups,[34-36] collectively suggest that non-thrombolytic anti-ischaemic treatment is likely to be beneficial only in patients with high potential for recurrent ischaemia, such as non-Q-wave infarction patients.

The serial echocardiographic findings in the subset of patients with transmural infarction suggest that the effect of nifedipine in reducing afterload may limit the expansion of the infarct zone during the ten days after an infarction. Although early expansion of the infarct is associated with an early increase in morbidity and mortality and the late development of left ventricular aneurysms,[12-14] the number of patients in the present trial with infarct expansion is too small for a difference in clinical outcome to be detected even if one were present. In addition, our population included many patients with inferior infarctions, in whom the clinical significance of infarct expansion is uncertain. A recent controlled study showing that intravenous glyceryl trinitrate and early intra-aortic balloon counterpulsation in patients with extensive anterior infarctions and low ejection fraction reduce the expansion into the non-infarcted area also suggests that afterload reduction may favourably influence the remodelling of the ventricular cavity that occurs after infarction.[37] Other agents which reduce afterload have been reported to have a favourable effect on infarct expansion including glyceryl trinitrate in humans[38] and captopril in rats,[39] suggesting that the afterload reduction itself may be the mechanism for this effect.

The time course of myocardial necrosis in human beings seems to be rapid, and interventions designed to limit infarct size should be started as early as possible.[40] The mean time between the onset of chest pain and treatment in this study was 8 (0·2) hours, primarily because the study design required baseline thallium and gated blood pool scans before the start of treatment in order to assess the effect of the agent on left ventricular function and the thallium scintigraphic definition of infarct size relative to the region at risk. The additional delay introduced by these baseline studies may have limited our ability to demonstrate a treatment benefit. Nevertheless, the analysis of the patient subset that received treatment within six hours, as well as previous studies[15-17] in which nifedipine treatment was initiated 4–6 hours after the onset of pain, also showed no benefit of nifedipine. At the present time, the collective results of the randomised nifedipine trials demonstrate no significant clinical benefit of nifedipine given in low or high doses.

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Assessment of left ventricular performance during percutaneous transluminal coronary angioplasty: a study by intravenous digital subtraction ventriculography

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ABSTRACT Left ventricular performance during percutaneous transluminal coronary angioplasty was assessed in 52 patients by intravenous digital subtraction ventriculography. After injection of contrast into the right atrium ventriculograms were obtained before and during balloon inflation. In 37 patients they were also obtained after the procedure. A 12 lead electrocardiogram was monitored throughout. During balloon inflation the left ventricular ejection fraction fell (from 73% to 57%) in all but one patient; the decreases in patients with single vessel or multivessel disease were similar. The fall in left ventricular ejection fraction during percutaneous transluminal coronary angioplasty of the left anterior descending artery (19%) was significantly greater than that during balloon inflation in the right coronary (10%) or circumflex (8%) coronary arteries. It also reduced anterobasal, anterior, and apical segmental shortening while right coronary percutaneous transluminal coronary angioplasty affected inferior and apical segments. In 33 (63%) patients the ST segment was altered during balloon inflation. The fall in left ventricular ejection fraction correlated significantly with the magnitude of both ST segment elevation (r = 0·637) and ST depression (r = 0·396). Left ventricular ejection fraction and regional wall motion returned to baseline values after the procedure.

Balloon inflation during percutaneous transluminal coronary angioplasty produces considerable abnormalities of global and regional left ventricular performance and this indicates the presence of myocardial ischaemia, which may not be apparent on electrocardiographic monitoring. Intravenous digital subtraction ventriculography is useful for monitoring left ventricular performance during controlled episodes of coronary occlusion produced by balloon inflation.

The emergence of percutaneous transluminal coronary angioplasty has provided an attractive setting in which to study left ventricular performance during short, controlled and reversible episodes of myocardial ischaemia.[1] Earlier studies used either M mode[2 3] or cross sectional echocardiography,[4–6] or direct cine left ventriculography.[7–9] These studies demonstrated the effect of balloon occlusion on global and regional left ventricular function. But both these techniques have limitations during percutaneous transluminal coronary angioplasty.

Echocardiography, although ideal for repeated or continuous studies, is dependent on patient suitability and operator expertise. The supine position of the patient on a catheter laboratory table is not always ideal for producing acceptable echocardiograms.[5 6] Direct cine left ventriculography requires the insertion of a second arterial catheter, which makes the percutaneous transluminal coronary angioplasty procedure more invasive. Furthermore, a direct intraventricular injection of contrast medium frequently provokes ventricular extrasys-

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toles which makes selection of cine frames for analysis of volume and wall motion difficult.[10 11]

For these reasons we have chosen to study left ventricular performance during percutaneous transluminal coronary angioplasty by intravenous digital subtraction left ventriculography. This technique produces diagnostic left ventriculograms from central venous contrast injection. Previous studies have demonstrated a high degree of correlation with direct cine ventriculograms when left ventricular volumes[10 11] and regional wall motion[12 13] measured by the two techniques were compared. Additional central venous cannulation does not significantly increase the invasiveness of percutaneous transluminal coronary angioplasty and contrast injection by this route is less likely to provoke extrasystoles.

We therefore report the first use of intravenous digital subtraction ventriculography in the examination of left ventricular contraction during percutaneous transluminal coronary angioplasty. We examined changes in global and regional left ventricular function in relation to alterations in the ST segment during electrocardiographic monitoring and we compared results in patients with single and multiple vessel coronary disease.

Patients and methods

PATIENTS

We studied 52 patients (45 men and seven women; mean age 53 (range 39–73)). All patients had stable but limiting angina despite medical treatment. Their regular medication, which included nitrates, calcium antagonists, and in 47 patients a β adrenergic blocking agent, was continued. No patient was taking digoxin and none had evidence of valve disease.

A resting electrocardiogram showed sinus rhythm in all cases with no evidence of bundle branch block. An electrocardiogram recorded during either spontaneous chest pain or a symptom limited treadmill exercise test had shown evidence of myocardial ischaemia in all patients as indicated by an alteration of at least 1 mm in the ST segment.

CORONARY ANATOMY

Previous diagnostic coronary arteriography had demonstrated single vessel disease, defined as at least an estimated 70% reduction in luminal diameter, in 37 patients. Twelve of the remaining 15 patients had two vessel and three had three vessel disease. In all but one patient the right coronary artery was the dominant vessel, giving rise to the posterior descending artery.

LESIONS ATTEMPTED

Percutaneous transluminal coronary angioplasty was attempted in the left anterior descending coronary artery in 35 patients, the right coronary artery in seven, and the circumflex artery in eight patients (including the one patient with a dominant circumflex system). The remaining two patients had percutaneous transluminal coronary angioplasty to lesions in a diagonal artery. There were no occluded vessels and in all cases the target stenoses allowed anterograde flow of contrast. The lesions ranged in severity of luminal narrowing from 60% to 99% (mean 92%).

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY PROTOCOL

Patients were studied during elective single vessel angioplasty. Two hours before the procedure they were given oral premedication with a long acting nitrate, calcium antagonist, and either lorazepam or intramuscular papaveretum.

Angioplasty was performed via the femoral approach. An intravenous bolus of heparin (100 IU/kg) was given at the start of the procedure together with atropine (up to 1·2 mg) if the heart rate fell below 50 beats/min. We used non-ionic contrast medium, steerable guide wires, and balloon catheters with diameters varying from 2·5 to 3·5 mm. The number of balloon inflations ranged from 2 to 12 (mean 5). Inflation pressures ranged from 505 kPa (5 atm) for initial inflations, up to 1212 kPa (12 atm) (mean 808 kPa (8 atm)). Inflation lasted for 15—95 seconds (mean 57 seconds), and the mean total duration of inflation was 162 seconds.

ELECTROCARDIOGRAPHIC MONITORING

Throughout the percutaneous transluminal coronary angioplasty procedure a standardised 12 lead electrocardiogram was monitored by a Seimens Elema Mingograf 804 and Mingograf 62 with a frequency response of 0·05–100 Hz. In order that the chest electrodes did not interfere with fluoroscopy during the procedure, we used Medicotest (A-50-VS, Cambmac) electrodes. The electrocardiogram was recorded at 25 mm/s immediately before and throughout each balloon inflation. Balloon inflation and deflation were marked on the electrocardiogram, which was recorded at the same paper speed until any changes had resolved.

DIGITAL SUBTRACTION VENTRICULOGRAPHY

A 5 French pigtail catheter (Superflow, Cordis) was inserted via the femoral vein and the tip was positioned in the right atrium. For each ventriculogram, 40 ml of non-ionic contrast (Omnipaque, Nycomed; iodine concentration, 350 mg/ml) was injected at a rate of 17 ml/s. We allowed seven seconds after the onset of contrast injection for transit of the contrast bolus through the pulmonary circulation and its subsequent arrival in the left ventricle. A digital ventriculogram was then acquired, in held inspiration, in a 30° right anterior oblique projection. Images were acquired at 12·5 frames per second on to a 256 × 256 pixel matrix using a Siemens Digitron connected online to a Siemens Elema Angioskop D imaging system. Acquisition times ranged from five to 10 seconds. The digital information was transferred on to hard computer disc and then to magnetic tape for subsequent recall and analysis. Ventriculograms were performed before the percutaneous transluminal coronary angioplasty procedure and after either 20 seconds (28 patients) or 60 seconds (24 patients) of balloon inflation. Thirty six patients were studied during the third balloon inflation. Of the remainder, one was studied during the second inflation, eight during the fourth, three during each of the fifth and sixth, and one during the eighth balloon inflation.

A third ventriculogram was performed in 37 patients immediately after the percutaneous transluminal coronary angioplasty was completed. In all cases, this was undertaken within 15 minutes of the ventriculogram acquired during balloon inflation and when the electrocardiogram had returned to normal.

DATA ANALYSIS

Electrocardiography

The deviation of the ST segment was measured 80 ms after the J point, a change of at least 1 mm being regarded as important. Leads V2—V5 were regarded as representing the left anterior descending coronary territory while leads II, III, and aVF were taken to reflect the distribution of the right coronary artery. The territory of the circumflex artery was represented by leads I, aVL, and V6. The maximum ST alteration in any lead was recorded.

Ventriculograms

Each digital acquisition was recalled on to hard disc and reviewed to identify the end diastolic and end systolic frames that were suitable for analysis. Extrasystoles were excluded. End diastolic frames were identified by an R wave marker. The subsequent end systolic frame was identified visually as that frame with minimum left ventricular dimensions. Left ventricular volume was identified by an area-length method[14] and ejection fraction was derived.

For analysis of left ventricular wall motion we used a method that does not make assumptions about left ventricular geometry.[15] Unlike the centre-line method it does not require identification of the apex of the ventricle. In this study, this was an advantage because location of the left ventricular apex is difficult in patients with coronary disease, who are likely to have segmental contraction abnormalities, especially during percutaneous transluminal coronary angioplasty. End diastolic and end systolic frames were outlined by hand. We took care to draw the end systolic outline outside the papillary muscles. We used a computer program to translate the two outlines so that the centres of each aortic valve plane could be superimposed. A series of radii were then drawn every 8°, from the edge of the aortic valve plane of the end diastolic frame, in a clockwise sweep, to the opposite aortic plane edge. These radii had their centre at the geometric centre of gravity of the

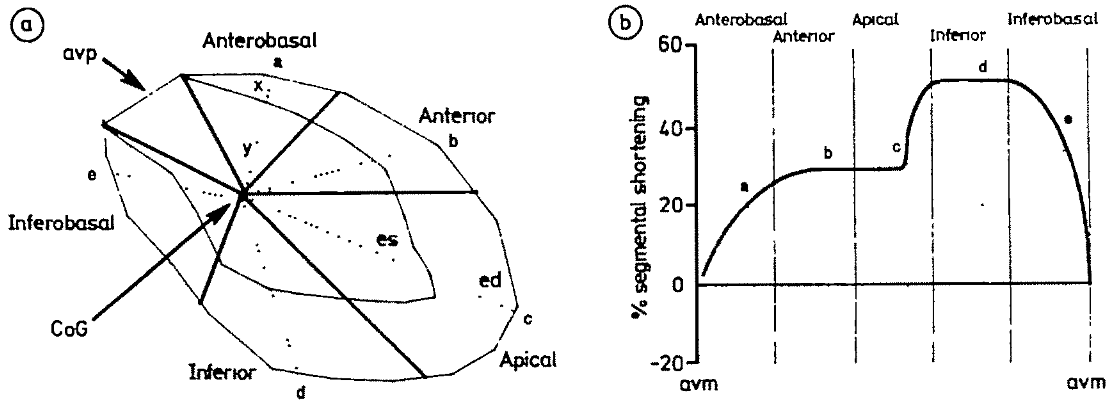

Fig 1 *Schematic representation of method to quantify regional left ventricular contraction. Sample radii (a–e) are shown for each left ventricular segment. Percentage segmental shortening (for example radius a) = x/x + y × 100. CoG, centre of gravity of end systolic frame; avp, aortic valve plane; es, end systolic outline; ed, end diastolic outline Percentage shortening for each radius plotted on a wall motion graph. avm, aortic valve margin.*

Table 1 *Left ventricular segmental shortening (percentage regional shortening (SD)) before percutaneous transluminal coronary angioplasty (52 patients)*

LV segment	*Regional shortening*	*Normal range*
Anterobasal	35 (12)	28–40
Anterior	36 (13)	30–45
Apical	46 (16)	42–62
Inferior	47 (13)	40–58
Inferobasal	8 (13)	0–20

end systolic frame. We calculated the percentage shortening of each radius, from the end diastolic to the end systolic outline (fig 1a). This was then represented as a point on a wall motion plot, showing percentage shortening for each radius in turn, in a clockwise sequence beginning at the upper limit of the aortic valve plane. The left ventricular perimeter was divided into five equal radial segments to represent the anterobasal, anterior, apical, inferior, and inferobasal left ventricular regions. The percentage shortening of the radii in each of these five segments was averaged to quantify regional contraction (fig 1b).

STATISTICAL ANALYSIS

We used Student's paired *t* tests to examine left ventricular ejection fraction and regional shortening before, during, and after percutaneous transluminal coronary angioplasty. We used unpaired *t* tests to compare patient subgroups with lesions of the left anterior descending, right, or circumflex arteries and with single or multivessel disease. Simple correlation and regression analysis was used to relate changes in left ventricular ejection fraction to ST segment deviation.

The study was approved by the ethics committee of the National Heart and Chest Hospitals and all patients gave written, informed consent.

Results

PRACTICAL CONSIDERATIONS

We obtained ventriculograms that were suitable for analysis from all 52 patients. Patients were required to hold inspiration for up to 10 seconds to allow data acquisition during balloon inflation, but this was not difficult.

Table 2 *Left ventricular ejection fraction (% (SD)) in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) of the left anterior descending, right, and circumflex coronary arteries*

Vessel dilated (cases)	*Before PTCA*	*During PTCA*	*p*
LAD (35)	74 (8)	55 (13)	< 0 001
RCA (7)	70 (14)	60 (14)	< 0 01
LCX (8)	69 (10)	61 (12)	< 0 01

LAD, left anterior descending; RCA, right coronary artery; LCX, circumflex.

The interval allowed for pulmonary transit of the contrast bolus was variable. In some patients, an interval of seven seconds after right atrial contrast injection was not sufficient for the arrival of contrast in the left ventricle, and so the first 30 to 50 frames of the ventriculogram were contrast free. In others, contrast was already clearing from the left ventricle when acquisition was started five seconds after injection. The duration of pulmonary transit was not related to either the heart rate or the degree of any pre-existing ventricular dysfunction.

COMPLICATIONS

There was ectopic activity during ventriculography in three patients in the study undertaken before percutaneous transluminal coronary angioplasty (supraventricular in two, ventricular in one) and in six others during balloon inflation (supraventricular in three, ventricular in three). In all these cases the extrasystoles were single and did not interfere with data analysis. Transient atrial fibrillation occurred in one patient immediately after injection of contrast for the pre-angioplasty ventriculogram. This was asymptomatic and did not recur during subsequent ventriculograms. Because this arrhythmia was short lived, it did not affect ventriculographic analysis.

Table 3 *Percentage shortening (mean (SD)) of left ventricular segments before and during percutaneous transluminal coronary angioplasty in patients undergoing dilatation of the left anterior descending, right, or circumflex coronary artery*

	LAD (35 patients)			*RCA (7 patients)*			*LCX (8 patients)*		
LV segment	*Before PTCA*	*During PTCA*	*p*	*Before PTCA*	*During PTCA*	*p*	*Before PTCA*	*During PTCA*	*p*
AB	37 (10)	28 (15)	< 0 002	33 (14)	30 (12)	NS	27 (15)	22 (14)	NS
A	39 (11)	13 (18)	< 0 001	38 (14)	34 (12)	NS	25 (18)	19 (25)	NS
AP	50 (14)	14 (19)	< 0 001	44 (19)	38 (20)	< 0 02	37 (20)	27 (26)	NS
I	48 (13)	46 (14)	NS	43 (17)	24 (18)	< 0 01	52 (11)	41 (14)	NS
IB	8 (13)	25 (17)	< 0 001	7 (11)	0 (14)	NS	10 (18)	18 (20)	NS

AB, anterobasal, A, anterior; AP, apical, I, inferior; IB, inferobasal, LV, left ventricular; LAD, left anterior descending, RCA, right coronary artery; LCX, circumflex.

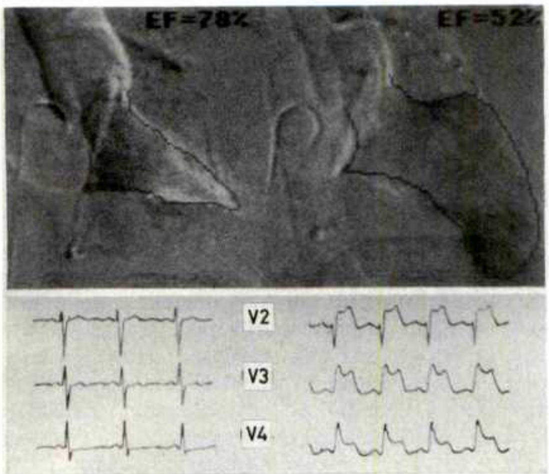

Fig 2 *End systolic outline of the left ventricle and electrocardiogram before (left) and during (right) balloon inflation in the left anterior descending coronary artery. Pronounced anteroapical akinesis was apparent during balloon occlusion associated with ST segment elevation in the leads reflecting activity in the anterior myocardium. EF, ejection fraction.*

LEFT VENTRICULAR PERFORMANCE BEFORE PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (TABLE 1)

The mean left ventricular ejection fraction of all 52 patients was 73% (range 51–90%). Table 1 shows the regional wall motion for each of the five left ventricular segments assessed and the normal range of regional shortening in 10 patients with normal left ventricular contraction.

EFFECT OF BALLOON INFLATION ON LEFT VENTRICULAR PERFORMANCE

Effect on left ventricular ejection fraction

During balloon inflation ejection fraction decreased in all but one patient. The mean fall in ejection fraction was from 73% to 57% ($p < 0\cdot001$). The decrease in left ventricular ejection fraction was no different in the 36 patients studied during the third balloon inflation (74% to 57%) than in the eight studied during the fourth inflation (70% to 59%) and the seven patients studied during subsequent inflations (72% to 56%).

Table 2 shows the effect on left ventricular ejection fraction of dilatation of the left anterior descending, right, and circumflex coronary arteries. The fall (19%) in left ventricular ejection fraction during dilatation of the left anterior descending artery was larger than that during balloon occlusion of the right (10%, $p < 0\cdot05$) and circumflex coronary arteries (8%, $p < 0\cdot01$).

EFFECT ON LEFT VENTRICULAR WALL MOTION (TABLE 3)

To assess the effect of balloon occlusion on segmental left ventricular performance, patients were grouped according to the site of the treated stenosis.

Dilatation of the left anterior descending coronary artery (35 patients, fig 2)

During balloon inflation regional shortening in the anterobasal, anterior, and apical left ventricular segments decreased. There was no change in inferior segmental contraction but inferobasal contraction increased.

Dilatation of the right coronary artery (seven patients, fig 3)

Balloon occlusion resulted in a fall in both inferior and apical contraction. There was no significant change in inferobasal, anterior, or anterobasal contraction.

Dilatation of the circumflex coronary artery (eight patients)

Balloon inflation did not produce significant changes in any left ventricular segment examined.

Dilatation of the diagonal vessel (two patients)

In these two patients balloon inflation produced falls in left ventricular ejection fraction of from 73% to 59%. The left ventricular segments affected were the anterior and apical regions, in which contraction was reduced from 35% and 40% to 14% and 5% respectively. Inferior contraction did not change

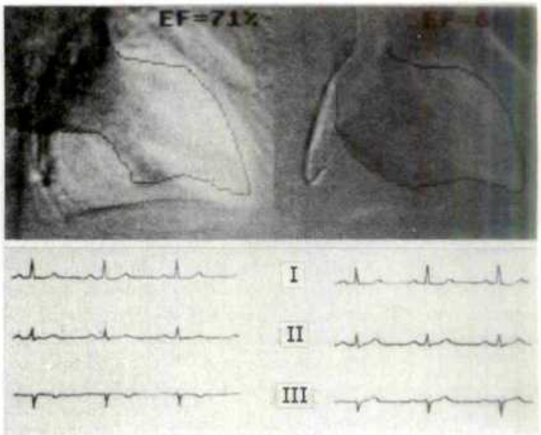

Fig 3 *End systolic outline of the left ventricle and electrocardiogram before (left) and during (right) balloon inflation of the right coronary artery. Inferobasal akinesis was in association with normalisation of a previously inverted T wave in lead III only. EF, ejection fraction.*

appreciably but inferobasal contraction increased from 3% to 25%.

ELECTROCARDIOGRAPHIC CHANGES

Although left ventricular ejection fraction fell during balloon inflation in 51 of the 52 patients, ST segment altered (>1 mm) in only 33 (63%). In thirty two patients ST elevation developed (mean 3·9 mm, range 1–9 mm). In all cases this occurred in leads coinciding with the myocardial territory supplied by the occluded artery. In 25 patients ST depression (mean 1·9 mm, range 1–3 mm) developed while in 24 patients both ST elevation and depression were seen.

Left ventricular ejection fraction before percutaneous transluminal coronary angioplasty was similar in the 32 patients in whom ST elevation subsequently developed during balloon inflation and the 20 in whom it did not (74% *vs* 72% respectively, NS). During balloon inflation, however, the fall in left ventricular ejection fraction was more pronounced in those patients with ST elevation (21%) than in those without (9%, p < 0·001). Furthermore, there was a significant positive correlation between the magnitude of ST segment elevation during balloon inflation and the reduction in left ventricular ejection fraction (r = 0·637, p < 0·001). Similarly, there was a positive though less strong correlation between the degree of ST segment depression and the fall in left ventricular ejection fraction (r = 0·396, p < 0·01).

SINGLE VS MULTIVESSEL DISEASE

Global left ventricular performance

The 37 patients with single vessel disease had a higher control left ventricular ejection fraction than the 15 patients with multivessel disease (75% vs 68% respectively, p < 0·02). During angioplasty left ventricular ejection fraction fell to 59% (p < 0·001) in those with single vessel disease and to 51% (p < 0·001) in those with multivessel disease. Although left ventricular ejection fraction during inflation was lower in those patients with multivessel disease (p < 0·05), the size of the fall in both groups was almost the same (16% vs 17% respectively, NS).

Electrocardiographic changes

The size of ST segment elevation during balloon inflation in the 37 patients with single vessel disease (2·4 mm) was no different from that in the remaining 15 patients with multivessel disease (2·3 mm, NS). Similarly, the degree of ST segment depression was no different in these two groups (0·8 mm *vs* 1·2 mm respectively, NS).

Regional left ventricular performance (35 patients, table 4)

Regional left ventricular performance was examined only in the 35 patients undergoing angioplasty of the left anterior descending coronary artery. Twenty seven of these had single vessel disease and eight had multivessel disease. Baseline left ventricular ejection fraction was similar in the two subgroups (76% *vs* 70%, NS). During balloon inflation left ventricular ejection fraction fell to 57% in those with single vessel disease and to 48% in those with multivessel disease. The size of the fall was similar in these two subgroups (19% *vs* 22%, NS).

Similarly, there was no difference between these two subgroups in the degree of ST elevation (3·2 mm *vs* 3·0 mm, NS) and ST depression (1·0 mm *vs* 1·0 mm, NS).

There was no difference in regional left ventricular contraction either before or during balloon inflation in the left anterior descending coronary artery between patients with single or multivessel disease (table 4).

Left ventricular performance after percutaneous transluminal coronary angioplasty (37 patients, table 5)

Thirty seven patients underwent intravenous digital subtraction ventriculography after percutaneous transluminal coronary angioplasty. In all cases the accompanying electrocardiogram had returned to its control state and ventriculography was performed within 15 minutes of the end of the percutaneous transluminal coronary angioplasty procedure.

Both left ventricular ejection fraction and regional left ventricular wall motion returned to the control

Table 4 *Left ventricular segmental contraction before and during percutaneous transluminal coronary angioplasty of the left anterior descending artery in patients with single (n = 27) or multivessel disease (n = 8)*

	Before PTCA			*During PTCA*		
LV segment	*SVD*	*MVD*	*p*	*SVD*	*MVD*	*p*
Anterobasal	37 (10)	36 (11)	NS	28 (15)	30 (15)	NS
Anterior	40 (10)	36 (13)	NS	15 (18)	8 (16)	NS
Apical	53 (10)	39 (20)	NS	17 (19)	3 (13)	NS
Inferior	48 (14)	47 (7)	NS	47 (14)	43 (12)	NS
Inferobasal	7 (12)	13 (14)	NS	25 (20)	24 (7)	NS

Values given are mean (SD) percentage shortening. SVD, single vessel disease, MVD, multivessel disease, LV, left ventricular.

Table 5 *Left ventricular ejection fraction and segmental wall motion before and after percutaneous transluminal coronary angioplasty (37 patients)*

	Before PTCA	*After PTCA*	*p*
LV ejection fraction	74 (9)	73 (8)	NS
LV regional shortening			
Anterobasal	37 (11)	35 (10)	NS
Anterior	38 (13)	36 (16)	NS
Apical	48 (16)	45 (20)	NS
Inferior	49 (13)	49 (17)	NS
Inferobasal	8 (15)	9 (15)	NS

Values are mean percentage (SD) LV, left ventricular.

value after the procedure. Fifteen patients were not studied after percutaneous transluminal coronary angioplasty. In nine cases the procedure was complicated by protracted coronary occlusion. This had resulted in a prolonged episode of myocardial ischaemia associated with considerable ST segment elevation. It was felt inappropriate to study these patients further. In three patients the angioplasty procedure itself had become protracted and had already used a large volume of contrast media. The addition of a third ventriculogram incorporating another 40 ml of contrast was deemed unwise. The three remaining patients not studied after percutaneous transluminal coronary angioplasty were recruited into another study that required them to undergo ventriculography during another balloon inflation. Ethical approval for the present study did not extend to four ventriculograms and thus the post-percutaneous transluminal coronary angioplasty study in these patients was waived.

Discussion

We report the first use of intravenous digital subtraction ventriculography in the assessment of left ventricular performance during coronary angioplasty. The validity of intravenous digital subtraction angiography has been established in studies that compared it with direct cine left ventriculography.[10-12] Correlation between the two techniques, in terms of both left ventricular volumes and ejection fraction, was good and digital subtraction angiography provoked fewer extrasystoles. Importantly, the degree of correlation between these techniques persisted in patients with impaired left ventricular function.[16 17] This is particularly relevant in patients undergoing percutaneous transluminal coronary angioplasty in whom left ventricular ejection fraction may fall profoundly during balloon inflation. Digital subtraction analysis and cine left ventriculograms gave corresponding assessments of regional left ventricular performance.[11-13]

In addition to validating the technique other studies have capitalised on the less invasive nature of intravenous digital subtraction analysis. Thus the technique has been used during exercise[18] and atrial pacing[19] in the investigation of patients with coronary disease, and as an outpatient assessment of left ventricular function.[20]

We found that this technique was suitable for the assessment of left ventricular performance during percutaneous transluminal coronary angioplasty. Although respiratory motion can often degrade the results of mask subtraction, this did not prove to be a problem, even during balloon coronary occlusion.

We used a non-ionic contrast agent (Omnipaque) for ventriculography. During intravenous digital subtraction angiography, passage of the contrast bolus through the pulmonary circulation can cause the patient to cough and this can interfere with image analysis. The risk of this happening is reduced by use of a non-ionic contrast and none of our 52 patients was affected. The use of non-ionic contrast enabled us to perform three ventriculograms in most patients. With conventional contrast agents such an amount of sodium, together with that required for the percutaneous transluminal coronary angioplasty procedure itself, might impose an appreciable ionic load.

The reduction in ectopic activity during intravenous digital subtraction angiography proved to be a distinct advantage; only nine of our 52 patients had extrasystoles. This is lower than the frequency reported by Norris *et al* in a study of 26 patients in whom nine developed extrasystoles during intravenous ventriculography.[10] This increased incidence may be explained by the use of an end hole rather than a multiple side hole catheter (either a Cournand or a Zucker). This would produce a more forceful single jet that is more likely to stimulate extrasystoles. Catheter recoil is also minimised and contrast mixing is improved with a pigtail catheter. There were few complications in our patients and only one of them developed transient atrial fibrillation.

Of the nine patients who developed extrasystoles in our study, these were supraventricular in five, and presumably directly related to atrial contrast injection. This finding accords with those of other workers who also found that atrial extrasystoles were more common than ventricular ones.[10]

Intravenous digital subtraction ventriculography did not significantly increase the invasiveness of the percutaneous transluminal coronary angioplasty. We routinely insert a femoral venous sheath during percutaneous transluminal coronary angioplasty in order to provide a route for intravenous administration of drugs or a temporary pacing catheter if required. The use of this sheath to insert a central venous pigtail catheter for contrast injection was preferable to cannulation of another peripheral artery, which would have been required if direct cine left ventriculography had been undertaken during percutaneous transluminal coronary angioplasty.

EFFECT OF BALLOON INFLATION ON GLOBAL LEFT VENTRICULAR PERFORMANCE

During balloon inflation in our 52 patients mean left ventricular ejection fraction fell from 73% to 57%. This is similar to the experience of other workers. Serruys *et al* noted a fall from 62% to 48% after 50 seconds of balloon occlusion.[7] Our fall in left ventricular ejection fraction in the whole group (16%) is similar to the decrease that Serruys *et al* reported (14%). Doorey *et al* noted a similar fall from 66% to 44% in patients not pretreated with nitrates.[8] After the administration of a nitrate left ventricular ejection fraction fell to only 49%. Bertrand *et al* noted a fall from 73% to 45%[9] which accords with our findings.

Previous studies did not examine global left ventricular performance in patients undergoing percutaneous transluminal coronary angioplasty of the circumflex coronary artery or right coronary artery. We showed that the reduction in left ventricular ejection fraction (19%) was significantly more pronounced during angioplasty of the left anterior descending coronary artery than during either balloon inflation in the right (10%) or circumflex (8%) arteries. This is compatible with our knowledge of the coronary circulation, where the left anterior descending coronary artery supplies most of the anterior left ventricular wall, septum, and apex. The small decrease in ejection fraction during angioplasty of the circumflex artery may relate to the 30° right anterior oblique projection that we used for image acquisition. This projection does not show the profile of the lateral wall of the heart and therefore abnormalities in this region may not be appreciated.

EFFECT OF BALLOON OCCLUSION ON REGIONAL LEFT VENTRICULAR FUNCTION

We found that balloon inflation in the left anterior descending artery predictably produced deterioration in the anterobasal, anterior, and apical segments. These findings accord with those of other workers. Doorey *et al* also demonstrated inferoapical dysfunction and noted that only anterobasal and inferobasal segmental shortening did not show a significant decrease in function.[8] Wohlgelernter *et al* similarly showed inferoapical dysfunction in addition to apical and septal changes.[6]

Interestingly, we also showed an appreciable increase in inferobasal contraction in this group. This feature has not been seen by others.[5 6] Doorey *et al*, however, noted an increase in shortening of the inferoapical and mid inferior segment during angioplasty of the left anterior descending coronary artery after the administration of glyceryl trinitrate compared with the shortening seen without glyceryl trinitrate.[8] All our patients routinely received a nitrate as part of their premedication and so we were not able to test the specific role of nitrates in improving segmental function distant to the ischaemic territory.

Few workers have examined the effects of balloon inflation during percutaneous transluminal coronary angioplasty of the right coronary artery. Alam *et al* demonstrated that during such a procedure abnormal wall motion was most noticeable posteriorly[3] while Hauser *et al* demonstrated deterioration in inferior contraction.[5] Visser *et al* studied only two patients during occlusion of the right coronary artery and showed that the resulting degree of left ventricular dysfunction was less pronounced than that during balloon inflation in the left anterior descending coronary artery.[4] This suggests that occlusion of the right coronary artery may have a less detrimental effect on global and regional left ventricular performance than occlusion of the left anterior descending coronary artery. Our results support this view because we found that left ventricular ejection fraction fell to a greater extent during balloon inflation in the left anterior descending coronary artery than during balloon inflation in the right coronary artery.

The effect of balloon occlusion of the circumflex artery on regional left ventricular performance has only been reported in two studies. Alam *et al* observed the effect of combined occlusion of both the left anterior descending and circumflex coronary arteries in one patient who developed reduced systolic excursion of both the septum and posterior walls.[3] Hauser *et al* showed no change in wall motion on cross sectional echocardiography during occlusion of the circumflex artery in one patient.[5] Our data on eight patients who showed no significant change in any segments during balloon inflation in the circumflex artery suggest that it is likely that lateral left ventricular segments rendered ischaemic by such occlusion are less amenable to either echocardiographic or ventriculographic assessment than anteroapical or inferior segments rendered dysfunctional by occlusion of the left anterior descending or right coronary arteries. This would also account for left ventricular ejection fraction during occlusion of the circumflex artery falling only to 61%, significantly less than during percutaneous transluminal coronary angioplasty of the left anterior descending coronary artery. It may be that abnormal wall motion during circumflex percutaneous transluminal coronary angioplasty would have been detected better in a left anterior oblique projection which images the lateral left ventricular wall than in the right anterior oblique projection.

The effects of balloon occlusion of the diagonal artery on segmental wall motion have not been described before. We only studied two patients, and both of them showed anterior and apical dysfunction together with augmentation of inferobasal contraction.

ELECTROCARDIOGRAPHIC CHANGES

In 63% of patients in the present study the ST segment altered during balloon inflation. This frequency is similar to that reported by others.[4 5 8] Because 12 lead electrocardiographic monitoring improves the detection of ischaemia during percutaneous transluminal coronary angioplasty[6] we used it in our study. Recent work has suggested that the ability to detect ischaemia during percutaneous transluminal coronary angioplasty may be enhanced by monitoring the intracoronary electrocardiogram recorded via the tip of the guide wire positioned distal to the coronary stenosis being treated.[21]

We have confirmed that the left ventricle can become dysfunctional in the absence of significant electrocardiographic change. We demonstrated, however, that the magnitude of global left ventricular ischaemia as manifest by a fall in left ventricular ejection fraction correlated significantly with the degree of ST segment elevation and to a lesser extent with ST segment depression. Thus ST segment alteration is an index of the degree of left ventricular ischaemia during percutaneous transluminal coronary angioplasty rather than merely an indicator of its presence.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY IN SINGLE VESSEL AND MULTIVESSEL DISEASE

Most previous studies have included only patients with single vessel disease. We found that up to 60 seconds of balloon inflation did not produce greater signs of ischaemia in patients with multivessel disease than in those with single vessel disease. The magnitude of ST segment change and the derangement of both global and regional left ventricular performance were no different in these two groups. It would be wrong to suggest that multivessel disease does not impose a greater ischaemic burden on the left ventricle than single vessel disease in patients undergoing percutaneous transluminal coronary angioplasty. The outcome after a complication during percutaneous transluminal coronary angioplasty in patients with multivessel disease is less favourable than that in patients with single vessel disease[22] and must reflect the consequences of coronary occlusion in the face of a reduced coronary reserve arising out of disease in other vessels. It may be that assessment of left ventricular performance after 60 seconds of balloon occlusion may have been too short for significant differences between these two groups to become apparent.

LEFT VENTRICULAR PERFORMANCE AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

We found that ejection fraction and regional wall motion returned to control values after the angioplasty procedure. This has been the experience of others who have similarly found no persistent dysfunction even after several long balloon inflations. Some workers found hypercontractility immediately after balloon deflation in segments that were dysfunctional during coronary occlusion.[4 6] These changes are apparent up to 20 seconds after balloon deflation but then rapidly return to normal. We did not see this overshoot phenomenon in regional wall motion. All patients were studied within 15 minutes of the completion of percutaneous transluminal coronary angioplasty but in no case did we perform the third ventriculogram within 20 seconds of the final balloon deflation.

CLINICAL IMPLICATIONS

We have shown that balloon inflation during percutaneous transluminal coronary angioplasty produces ischaemia manifest as profound but reversible abnormalities of global and regional left ventricular performance that may not be apparent with electrocardiographic monitoring. This is clinically relevant because it has been suggested that prolonged balloon inflation may reduce the rate of restenosis after successful percutaneous transluminal coronary angioplasty.[23] Some anxiety remains about the cumulative effect on the left ventricle of such prolonged episodes of coronary occlusion.[24 25] The examination of left ventricular performance by intravenous digital subtraction angiography during balloon inflation brings two benefits. In addition to providing valuable insight into the earliest effects of coronary occlusion, it may also allow a relatively non-invasive yet accurate assessment of techniques designed to limit myocardial ischaemia during percutaneous transluminal coronary angioplasty.

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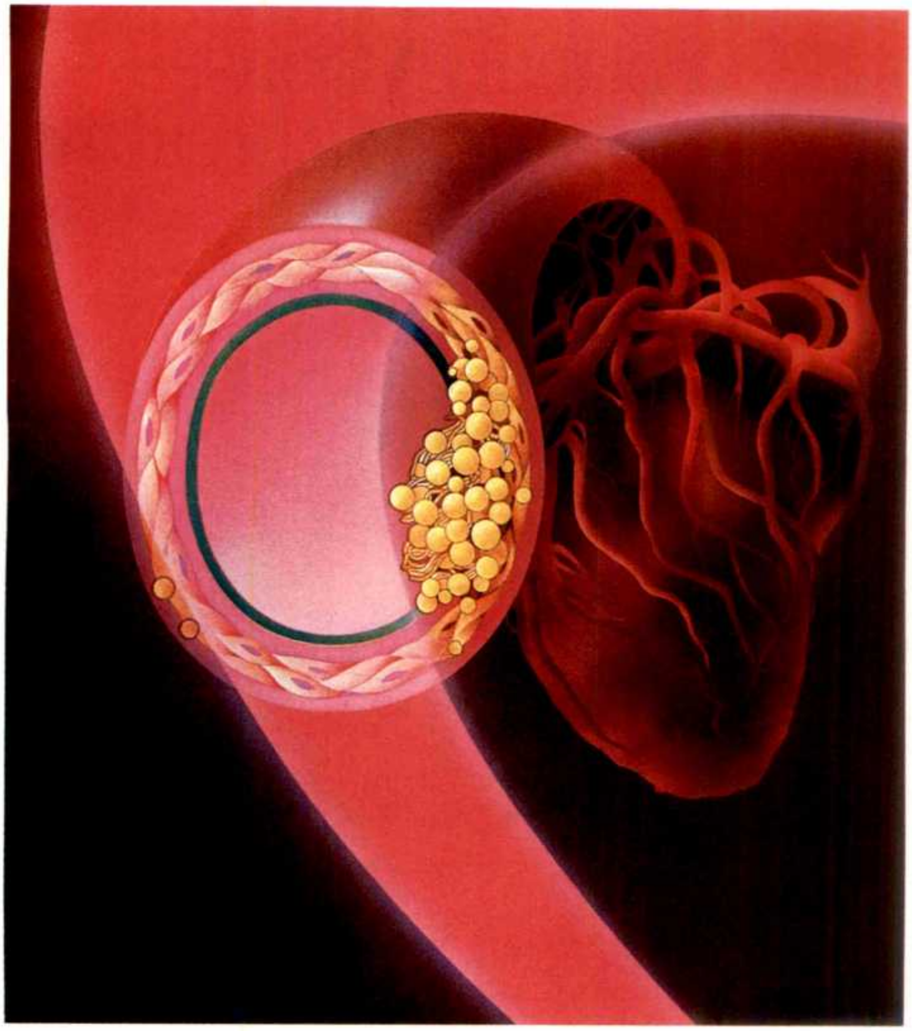

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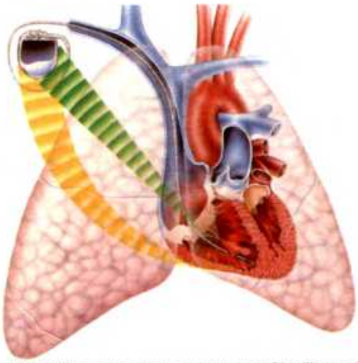

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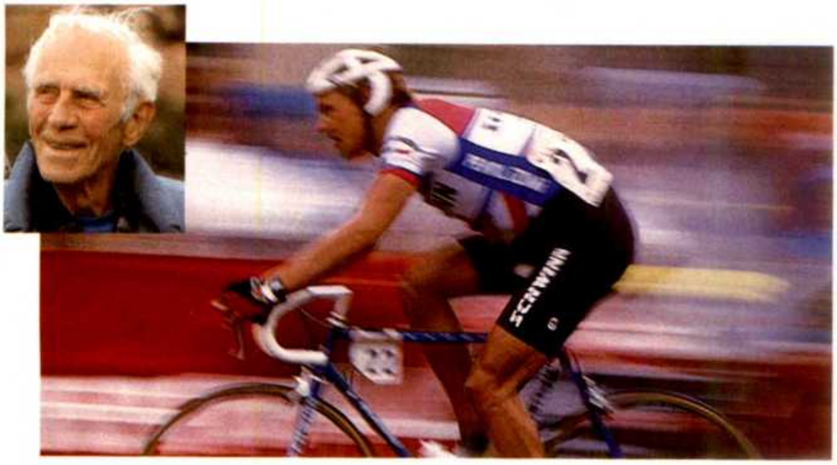

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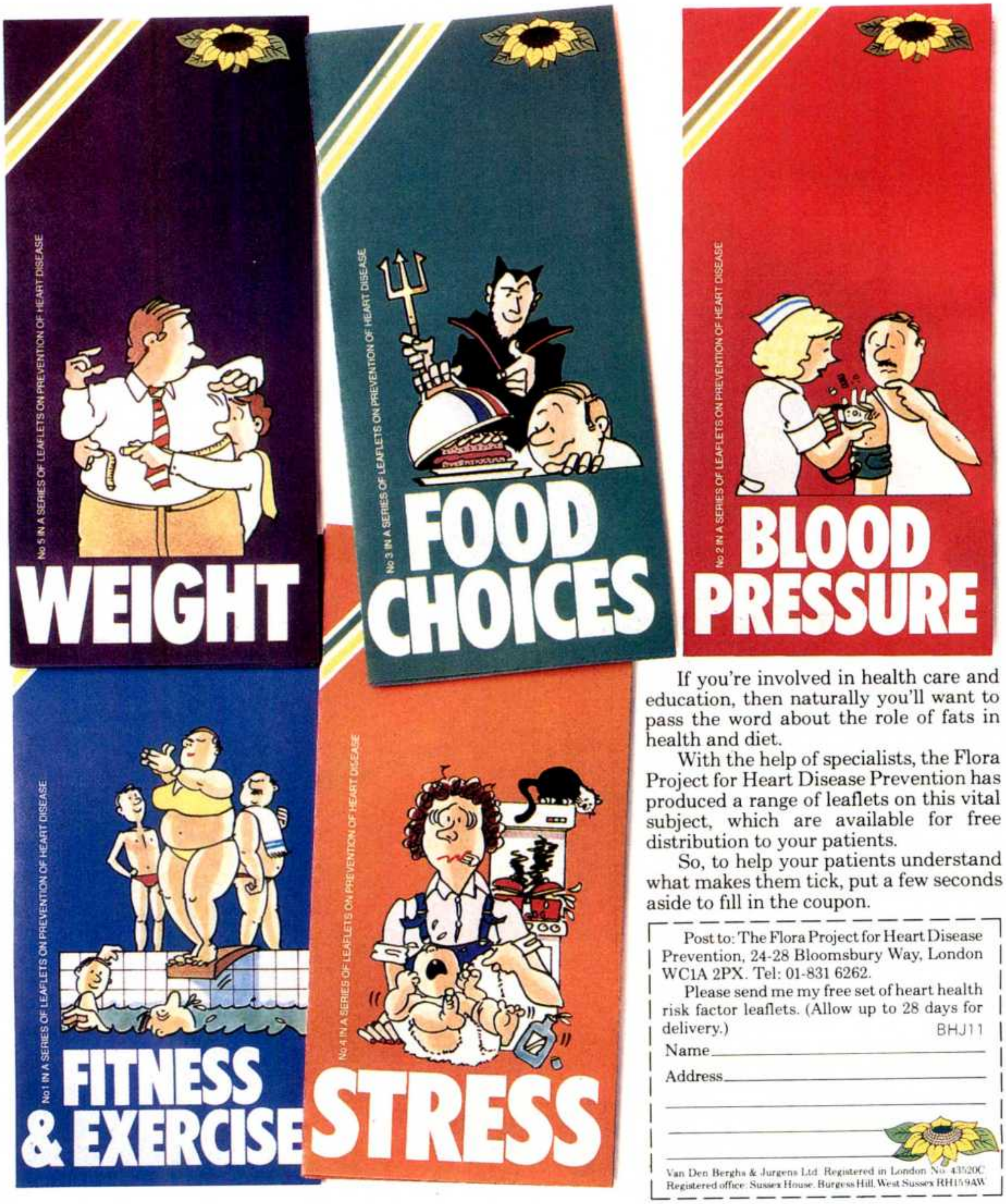
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Perforation thresholds and safety factors in in vivo coronary laser angioplasty

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SUMMARY Laser angioplasty can cause early (acute perforation) or late (stenosis or aneurysm) complications. To find how much intravascular laser energy can be delivered via a 100 μm core optical fibre passed down a balloon angioplasty catheter without causing angiographic abnormalities up to 10 days later, argon laser energy was delivered percutaneously under radiographic screening to the coronary circulation of 12 normal closed chest dogs. With the balloon inflated, sequential laser pulses were delivered to the same site. Angiograms were recorded before, immediately, and again at one week, after laser delivery. There were two laser-induced perforations (both fatal). Mechanical perforation with the 100 μm fibre occurred four times, but there were no haemodynamic sequelae. To find the acute perforation threshold of similar sized arteries to energy delivered via the bare 100 μm core fibre, the tip of which was held in contact with the luminal surface, 32 argon laser pulses were delivered transluminally in vivo to separate sites in normal rabbit iliac and canine coronary arteries. The acute perforation threshold with energy delivered via the angioplasty catheter lay between 6 and 10 J and that without the balloon angioplasty catheter lay between 3 and 4 J. After delivery of up to 6 J via a balloon angioplasty catheter, there were no angiographic abnormalities at one week. Fibre optic transluminal delivery of laser energy may improve the primary success rate of, and perhaps widen the indications for, coronary angioplasty.

Since 1977 it has been possible to revascularise human myocardium percutaneously by balloon angioplasty.[1] Originally application of this technique was thought to be limited, but the indications for percutaneous transluminal coronary balloon angioplasty have widened. There are now only two main limitations to the technique. These are the ability of the operator to cross the anteromatous lesion with the guide wire and balloon, and restenosis, which occurs in about 30% of patients, usually within 3–6 months of the procedure.[2 3]

Laser energy can be delivered transluminally via an optical fibre introduced percutaneously to vaporise intraluminally some of the occluding atheroma. This should enhance the operator's ability to cross the lesion. Use of a laser in conjunction with balloon angioplasty ("laser-assisted balloon angioplasty") may extend the technique to those lesions which are not attempted because current angiographic preselection indicates that they are "uncrossable". Whether laser energy could reduce the limitation of restenosis is uncertain, but this possibility can be evaluated only if the laser technique becomes clinically applicable.

The safety of the technique depends on the ability to vaporise luminal atheroma without causing undue damage to the subjacent normal arterial wall. This requires a reliable intracoronary delivery system and the definition of the characteristics that will not cause either immediate vessel perforation or longer term thermal damage. There are reports of relatively high in vitro[4] and in vivo[5] vessel perforation rates in various normal and atheromatous models and the late appearance of aneurysms in arteries treated by laser.[6]

The present study had three aims. The first was to test in vivo a prototype system for the percutaneous transluminal delivery of laser energy to the coronary circulation. The second was to find the acute in vivo perforation threshold of arteries that were the same size as those of the human epicardial coronary circulation. Intravascular argon laser energy was

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delivered with the tip of a bare laser fibre deliberately positioned tangentially in contact with the luminal surface of the artery and then with the laser fibre tip protruding from within an inflated balloon angioplasty catheter, so as to minimise direct contact between the fibre tip and arterial wall. The third aim was to study the immediate and longer term radiographic effects of different argon laser pulses (identified in a previous in vitro study[7] as being appropriate for vaporisation of atheroma) delivered via the angioplasty catheter to the normal canine coronary circulation that might have a bearing on the late appearance of perforations, stenoses, or aneurysms. Thus we hoped to find conditions for the safe delivery of laser energy to the normal coronary circulation.

Methods

A Cooper Medical Aurora laser, capable of delivering up to 7 W of argon laser power, was coupled to a 100 μm core diameter optical fibre via an electronic shutter. The power output from the distal end of the fibre (1·0–3·0 W) was measured with a calorimeter and power meter, before and after each series of energy deliveries to each animal.

ENERGY DELIVERY BY BARE FIBRE

A left lateral thoracotomy was performed under general anaesthesia on two normal greyhounds. The left coronary artery was cannulated directly with the bare optical fibre and the tip was passed distally to different sites within its branches. The position of the fibre tip was checked by direct inspection of the laser's aiming beam (low power < 1 mW) at the site at which it was transilluminating the arterial wall (fig 1). At each arterial site, the fibre tip was deliberately positioned up against the luminal surface of the vessel, and a single laser pulse (the energy of which was varied from site to site) was delivered. The presence or absence of acute vessel perforation was then immediately assessed, by the presence or absence of blood leaking from the vessel. The animals were then killed and their hearts excised.

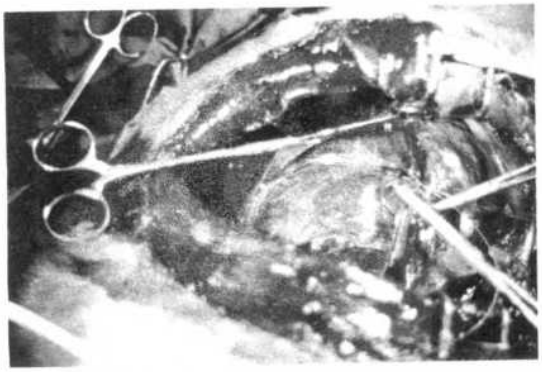

Fig 1 *Dog 1 at thoracotomy, with heart brought up on pericardial cradle. An optical fibre was inserted via an arteriotomy into left anterior descending coronary artery. There is laser transillumination from the fibre tip seen just below the tip of the central pair of forceps.*

The abdominal aorta and iliofemoral arteries were exposed by laparotomy in five anaesthetised rabbits. A carotid cut down was performed and the artery was cannulated with the bare optical fibre, which was passed via the descending aorta to the abdominal aorta, the wall of which could be transilluminated with the laser's aiming beam. The fibre tip was advanced to various different sites in both iliofemoral arteries (its exact position being ascertained from the aiming beam). At each arterial site the fibre tip was positioned in direct contact with the luminal surface of the vessel, and a single laser pulse (the energy of which was varied from site to site) was delivered. The presence or absence of acute vessel perforation was then assessed. The animals were then killed and the lasered vessels were excised.

Overall in both the rabbit and dog experiments, 32 separate laser pulses were delivered to 32 separate arterial sites. The range of pulse energies delivered was 0·2–7·0 J.

BALLOON ANGIOPLASTY CATHETER ENERGY DELIVERY

For the experiments with balloon angioplasty catheter energy delivery, twelve greyhounds were used. Each dog was anaesthetised and a cut down was performed to the left carotid artery, through which a 8·3F guide catheter was introduced under radiographic screening and advanced to whichever coronary ostium was most easily cannulated (the left in all but one). A pre-laser coronary angiogram was recorded.

The optical fibre was preloaded down the "through" lumen of a standard 4·3F 3·0 mm balloon angioplasty catheter and adjusted so that the fibre tip protruded from the catheter tip by 2–3 mm, and the device was inserted into the guide catheter. The sidearm of a Y connector previously attached to the proximal end of the balloon catheter was used for the infusion of Hartmann's solution down the "through" lumen alongside the optical fibre, at a pressure of 300 mm Hg and at a rate of 1·5 ml/min.

For the first three dogs we used balloon angioplasty catheters in which the "through" and balloon inflation lumen lay side by side. Thereafter, we used balloon angioplasty catheters with a "through" lumen that was central to and coaxial with the balloon inflation lumen.

Initial laser delivery and angiography

The fibre/catheter device was passed via the guide catheter under radiographic screening several centimetres into a major branch of a coronary artery. Energy was delivered according to the following protocol. A sequence of three separate laser pulses was delivered to the same site within the cannulated artery, in the following order: a 1 J pulse, a 2 J pulse, and then a 3 J pulse. For delivery of each individual laser pulse we used a set protocol.

(a) Radiographic contrast medium was injected to check vessel patency and integrity.
(b) The angioplasty balloon was inflated to occlude downstream blood flow.
(c) The Hartmann's perfusion was then turned on.
(d) The measured amount of laser energy was then delivered via the optical fibre during perfusion with Hartmann's solution.
(e) The angioplasty balloon was then deflated.
(f) The Hartmann's perfusion was then turned off.
(g) Radiographic contrast medium was injected to check vessel patency and integrity.

In this way, the laser energy was delivered under standardised conditions—the optical fibre being perfused locally with Hartmann's solution, and being held as centrally as possible within the vessel lumen so that contact time during the cardiac cycle between fibre tip and arterial wall would be minimised. The fibre/catheter device was then removed from the guide catheter, inspected for damage, and a post-laser coronary angiogram was recorded. The guide catheter was removed, the carotid artery was repaired, and the skin was sutured. The dogs were then allowed to recover from the anaesthetic.

Repeat angiography at 7–10 days

The dogs were re-anaesthetised 7–10 days later. After a repeat carotid cut down a 8·3F guide catheter was introduced under radiographic screening to the ostium of the coronary artery to which laser energy had previously been delivered, and a 7–10 day post-laser coronary angiogram was recorded. Whenever it was possible either the contralateral or the other major branch of the left coronary artery was then cannulated and a pre-laser angiogram was recorded. The fibre/catheter device was then passed into the newly cannulated (and previously "un-lasered") coronary artery branch. A single 5 J laser pulse was delivered to this arterial branch, by the same delivery sequence as described above. On one occasion two sequential 5 J laser pulses were delivered to the same site.

The fibre/catheter device was then withdrawn from the guide catheter and a post-laser coronary arteriogram was recorded. If the dog survived, ventricular fibrillation was induced with intracoronary potassium chloride. The animal's chest was then opened and the pericardium was incised. A careful inspection was made for any free blood, fluid, thrombus, or any epicardial or pericardial damage or adhesions, particularly in the region of the vessels treated by laser. The animals' hearts were then excised.

In all the canine experiments, both initially and at repeat angiography, the dogs' electrocardiograms were continually monitored, and recordings were taken before and after laser treatment.

Results

DELIVERY OF ENERGY BY BARE FIBRE

Table 1 shows the results of the rabbit and open chest dog experiments in which the bare optical fibre was used. Vessel wall perforation never occurred with the 22 laser pulses whose energies were 3 J or less. Three out of five 4 J laser pulses caused acute vessel wall perforation, and all five of the laser pulses of 5 J or more caused acute vessel wall perforation.

DELIVERY OF ENERGY BY BALLOON ANGIOPLASTY CATHETER

Table 2 shows the overall results of the closed chest dog experiments in which the optical fibre was passed within the inflated balloon angioplasty catheter.

Short term and long term effects of cumulative 1, 2, and 3 J pulses

Of the ten dogs that received sequential delivery of three laser pulses (1 J, 2 J, then 3 J) to the same site in their coronary circulation, nine had normal immediate post-laser coronary angiograms and unchanged electrocardiograms. Although the cardiovascular state of the first and third of these nine was satisfactory and stable for several hours after the procedure, their ventilation was not (it took over an hour to wean both of them off the ventilator), and both were found dead the following morning. Post-

Table 1 *Energy delivery by bare fibres*

	Number of perforations/pulses delivered					
Pulse energy (J)	*Dogs (2 W)*	*Rabbits (1 W*	*1·5 W*	*2 W*	*3 W)*	*Total*
0·2	0/1	..		.	.	0/1
0·5	0/2	..	..	.		0/2
1·0	0/2	0/2	0/1	0/1	0/2	0/8
2·0	0/1		0/1	0/1	0/2	0/5
3·0	0/1		0/1	0/1	0/3	0/6
4·0	1/1		0/1	..	2/3	3/5
5·0	1/1	1/1	..		..	2/2
6·0	.	..		2/2	..	2/2
7·0		..		1/1		1/1

Table 2 *Energy delivery by balloon angioplasty catheter*

	Angiography				
Dog	*Immediate*	*Repeat*	*Perforation*	*Mode of death*	*Laser power (W)*
3	N	–	Nil	<12 h anaesthetic	2
4	Perf 3 J	–	Laser	Immediate laser	1·5
5	N (MP)	–	Mechanical	<12 h anaesthetic	1·5
6	N	N	Nil	7 days, killed	3
7	N (MP)	N	Mechanical	7 days, killed	1
8	N (MP)	N	Mechanical	7 days, killed	2·5
9	N (5 J)	–	Nil	Immediate, killed	1·5
10	N	N	Nil		1
	Perf 5 + 5 J		Laser	10 days, laser	2·5
11	N (5 J)	–	Nil	Immediate, killed	1·5
12	N (MP)	N	Mechanical	10 days, killed	2
13	N	N	Nil	7 days, killed	2
14	N	N	Nil	9 days, killed	2

MP, angiographic evidence of mechanical perforation; Perf, perforated; N, normal; (5 J), single 5 J pulse delivered at initial angiography.

mortem examination did not find any blood in the pericardial space or any other evidence of laser perforation or myocardial damage. Postmortem angiograms of the lasered vessel were normal.

Thereafter the anaesthetic technique was altered. The other seven dogs recovered and survived without any complications. Repeat angiography at 7–10 days of the previously lasered vessels were all normal, and there was no change in the dogs' electrocardiograms. Postmortem examination of these seven dogs did not show any macroscopic evidence of laser perforation.

In the second of the ten dogs that received the sequential laser pulses (1 J, 2 J, then 3 J) to the same intracoronary site, laser perforation occurred after the 3 J pulse. During the post-laser angiogram the dog went into ventricular fibrillation and died. Postmortem macroscopic inspection of the laser perforation site (fig 2) showed a discrete hole with little surrounding damage. After withdrawal of the fibre/catheter device it was apparent that the tip of the optical fibre had been pushed back (by about 1·5 mm) relative to the catheter tip, and that the balloon had become deformed into a banana shape such that the fibre tip was protruding obliquely from the catheter tip. In this balloon angioplasty catheter the through and balloon inflation lumens lay side by side. Such balloon deformation with oblique displacement of the fibre tip did not occur with balloon angioplasty catheters with a central through lumen that ran coaxially within the balloon inflation lumen.

Short term effects of 5 J pulses

In two dogs (9 and 11), because of radiographic contrast induced electrocardiographic instability, a single 5 J pulse was delivered at the initial general anaesthetic, and the dogs were killed immediately. In a third dog (10) it was possible to intubate the other main left coronary artery branch at repeat angiography ten days later. In this third dog two separate 5 J laser pulses were delivered to the same site.

In all three, there was no difference between the pre- and post-laser angiograms or electrocardiograms after the single 5 J pulse. In dog 10, however, perforation occurred after delivery of the second 5 J laser pulse to the same site (cumulative energy dose of 10 J) (fig 3). A haemopericardium formed, but the heart continued to beat. After about 30 minutes (during which there were no arrhythmias), the animal was killed by infusion of intracoronary potassium chloride. Postmortem macroscopic inspection of the laser perforation site (fig 4) showed a larger hole with more widespread

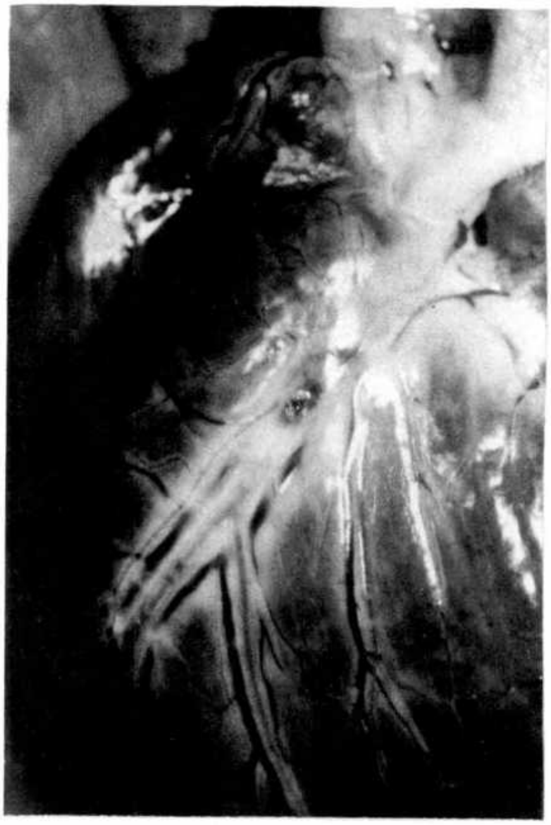

Fig 2 *Pathological specimen from dog 4 showing left anterior descending coronary artery after a 3 J laser pulse (cumulative dose of 6 J) delivered when the laser fibre had been inadvertently positioned obliquely within the vessel lumen. Compare with fig 4.*

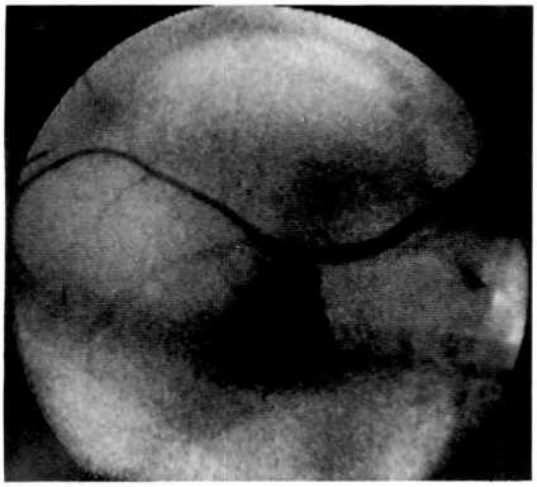

Fig 3 *Post-laser left anterior descending coronary angiogram in dog 10 after delivery via an angioplasty catheter of two 5 J pulses to the same site. Contrast medium can be seen spurting from underside of artery, and beginning to collect in the pericardial space.*

surrounding damage than was seen after the laser perforation with the inadvertently obliquely positioned fibre tip. Postmortem examination of the other two vessels (which had each received only one 5 J pulse) did not show macroscopic evidence of laser perforation.

PERFORATIONS

Throughout the delivery of the 34 different laser pulses, laser perforation only occurred on two occasions (both described above). On four other occasions there was radiographic evidence of mechanical perforation of the vessel wall by the protruding optical fibre tip during manipulation of the fibre/catheter device within the coronary circulation before any laser energy was delivered. This was shown by the appearance of a small blush of extravasated contrast medium to one side of the vessel when contrast was injected immediately before delivery of the first laser pulse (figs 5a–d).

On all four occasions there were no haemodynamic consequences, the fibre/catheter device was manipulated a centimetre or so past the point of mechanical perforation, and the sequence of laser pulses was delivered to this more distal site as described above. In all four cases the immediate post-laser angiograms were normal. Three of the four animals survived to 7–10 days, and at this time repeat angiograms of the previously lasered vessels were normal, with no evidence of the previous mechanical perforation. In one of these three dogs, postmortem examination showed a small subepicardial haematoma (fig 6). In the other two there was no postmortem evidence of vessel perforation.

One of the four instances of mechanical perforation occurred in a dog in which death was attributed to anaesthesia. Postmortem examination showed a small subepicardial haematoma at the site of mechanical perforation, but no macroscopic evidence of laser damage, nor any blood, clot or adhesions within the pericardium. A postmortem angiogram of this lasered vessel was normal.

CATHETER DAMAGE

On three occasions the fibre/catheter device was damaged during the procedure. The first occasion (already described) was when the optical fibre tip became pushed back relative to the catheter tip, such that the fibre protruded obliquely causing laser perforation.

On the other two occasions, during delivery of the first laser pulse the balloon suddenly deflated and could not be reinflated. An internal perforation between the balloon and the through lumen had occurred and contrast medium had passed via the balloon into the through lumen and out into the lumen of the coronary artery. There were no haemodynamic or electrocardiographic consequences. On one occasion the fibre had retracted relative to the catheter (while it was being manipulated to the coronary circulation) such that its tip was entirely within the tip of the catheter and on the other occasion the fibre fractured within that part of the through lumen that traverses the balloon.

All three cases of catheter/fibre damage occurred with balloon angioplasty catheters in which the through and balloon inflation lumens ran side by side. Thereafter we used only balloon angioplasty

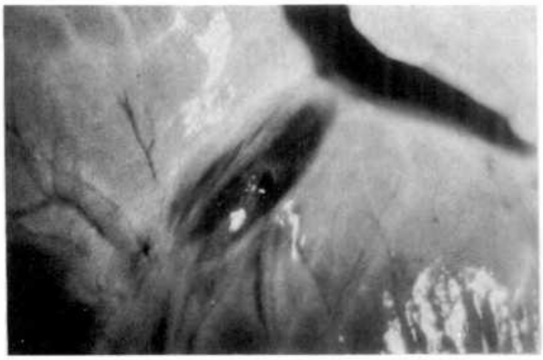

Fig 4 *Pathological specimen of the perforated left anterior descending coronary artery in dog 10. Perforation occurred after delivery, via an angioplasty catheter of two 5 J laser pulses. Compare with fig 2.*

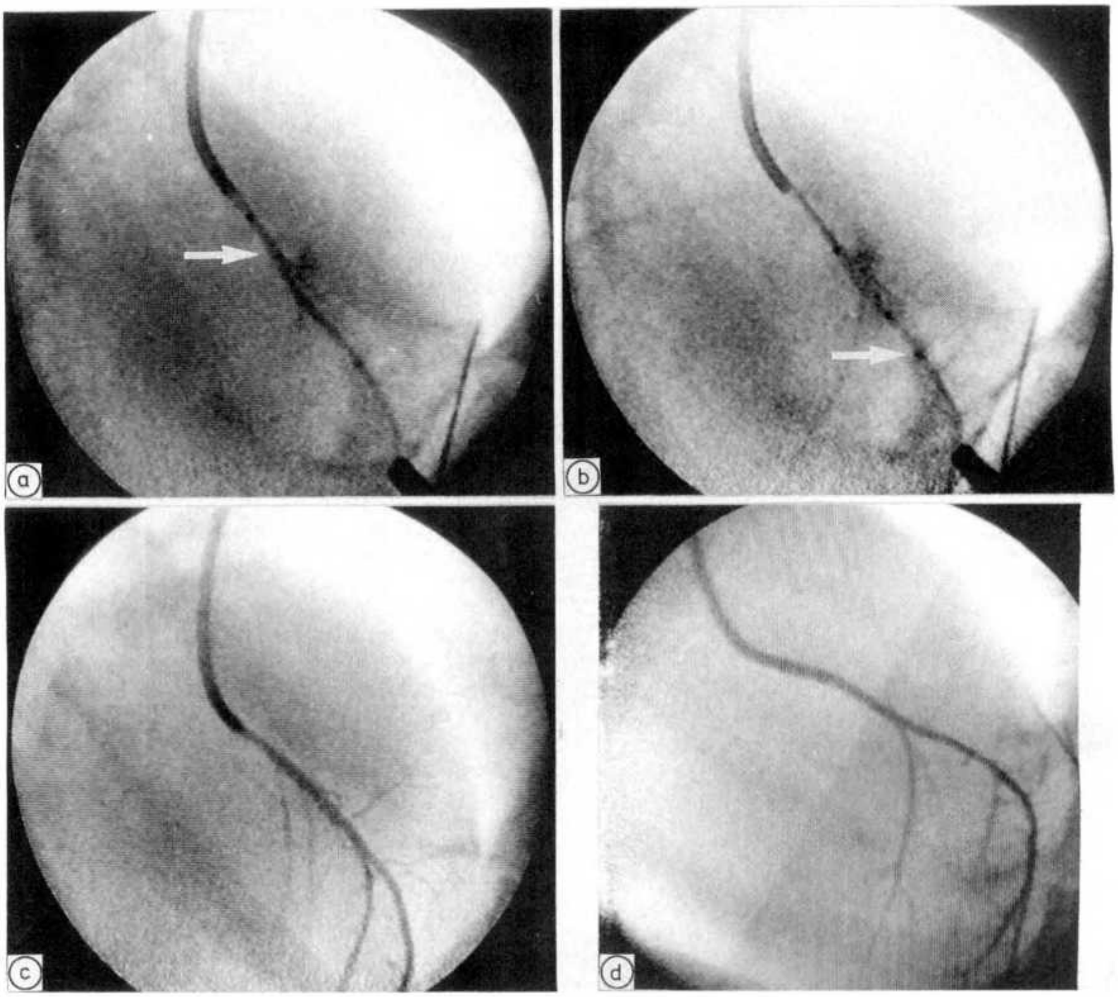

Fig 5 *Mechanical perforation in dog 12. (a) Showing blush of extravascular contrast medium to right of left anterior descending artery, just downstream from distal radiographic marker (arrowed) of balloon angioplasty catheter. (b) Fibre/catheter device manipulated distal to site of mechanical perforation (distal radiographic marker arrowed). (c) Immediate post-laser angiogram with no evidence of laser perforation or further extravasation from the mechanical perforation site. (d) Angiogram obtained 10 days after angioplasty showing no evidence of mechanical or laser damage.*

catheters with through lumens that were central and coaxial within the balloon inflation lumens, and no further catheter/fibre damage occurred.

Discussion

From a superficial examination of these data it might appear that the laser perforation threshold was higher when laser delivery was via an angioplasty catheter than when it was not. No definite conclusions can be drawn about this, however, as the presence or absence of a balloon angioplasty catheter was not the only factor that varied between delivery of energy by bare fibres and by balloon angioplasty catheters.

We used bare fibres to deliver 32 laser pulses to 32 separate sites on the luminal surface of 12 arteries during blood perfusion in open chest dogs or exposed rabbit iliac vessels. The acute in vivo argon laser perforation threshold lay between 3 and 4 J; energy density with this fibre is about 50 kJ/cm^2.

We used a balloon angioplasty catheter to deliver 34 laser pulses to 13 separate sites in 13 different coronary arteries: at two sites a single (5 J) pulse was

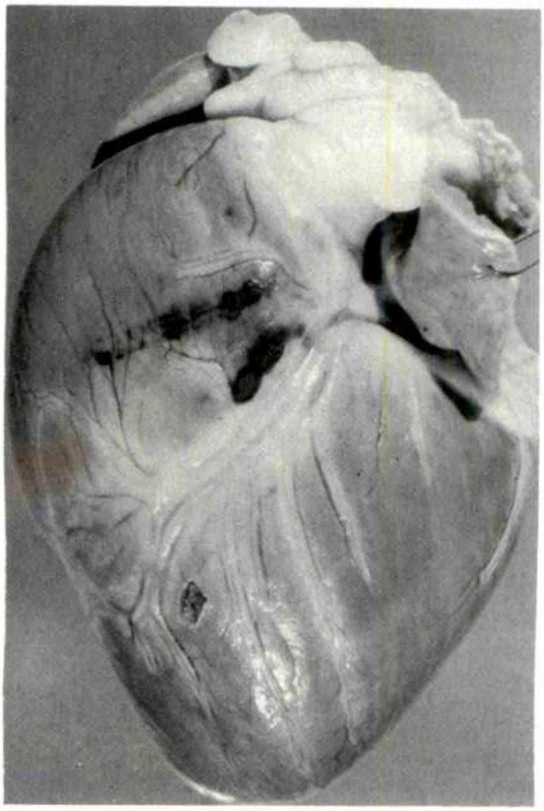

Fig 6 *Pathological specimen showing subepicardial haemotoma in dog 7. This was an incidental finding when the dog was killed one week after mechanical perforation that had no sequelae. (A myocardial block was excised from the apical region post mortem.)*

given, at one site two sequential pulses (2 × 5 J) were given, and at ten sites three sequential pulses (1 J, 2 J, and 3 J) were given. The laser pulses were given during Hartmann's perfusion in closed chest dogs. With one exception, laser energy of up to 5 J (single pulse) or 6 J (cumulative dose) at one site produced no immediate angiographic or electrocardiographic abnormalities; however, a cumulative dose of 10 J at one site produced immediate vessel perforation.

The exception was dog 4, in which laser perforation occurred after a 3 J pulse (6 J cumulative dose), and this was the only case in which deformation of the balloon had caused the fibre tip to protrude obliquely from the catheter tip. In all subsequent cases we used angioplasty catheters with a through lumen that was central and coaxial within the balloon inflation lumen, and inspection of the fibre/catheter system after laser delivery did not show any deformity or oblique protrusion of the fibre tip. In all we found a straight balloon with the fibre tip positioned centrally as it emerged from the catheter tip. Macroscopically, the perforation site in dog 4 (fig 2) was smaller and with less surrounding damage than that produced by 10 J in dog 10 (fig 4) when the fibre had remained central within the catheter tip.

Non-perforating laser pulses (of up to 3 J (single pulse) or 6 J (cumulative dose)), delivered via balloon angioplasty catheter resulted in no angiographic or electrocardiographic abnormalities at 7–10 days. The higher perforation threshold with the balloon angioplasty catheter must be the result of several factors, only one of which is the positioning of the fibre tip within the vessel lumen to reduce direct contact with the arterial wall during the cardiac cycle. Other factors are the use of closed chest dogs, sequential laser pulses, and Hartmann's perfusion with the balloon angioplasty catheter, as opposed to the use of open chest dogs, rabbit iliac vessels, single laser pulses, and blood perfusion with the bare fibre.

Initially open chest dogs were chosen so that direct intraluminal contact could be ensured and immediate vessel perforation recognised by direct visual examination. A range of pulse energies was used to find an approximate perforation threshold. Thereafter, for the sake of economy we used rabbit iliac arteries of similar size. Results were similar in both rabbits and dogs. Differences between the thermal damping of the open preparations (used with bare fibres) and that of the closed preparations (used with balloon angioplasty catheters) will influence the perforation threshold. The laser perforation in dog 4 at an energy level equivalent to the bare fibre perforation threshold, however, suggests that the thermal damping effect is not large.

To imitate clinical practice, we used closed chest dogs with balloon angioplasty catheters, and in all but two, sequential pulses were delivered to one site. In the two in which a single 5 J pulse (which exceeds the bare fibre perforation threshold) was delivered to a single site, perforation did not occur. This suggests that the higher perforation threshold with an angioplasty catheter may not wholly be the result of sequential pulses.

The presence of blood enhances argon laser vaporisation, including that caused radially from the central axis of the fibre tip.[8] This will have been a (perhaps major) contributory factor in the lower perforation threshold with the bare fibre. Because in clinical practice we would aim to minimise the lateral spread of thermal effect by delivering the laser energy in clear fluid we used perfusion with Hartmann's (to maintain intracoronary normokalaemia in the closed chest dogs). Dangerous localised intracoronary hyperkalaemia caused by argon laser induced haemolysis is unlikely.[9]

Although with our fibre/catheter device, mechanical perforation did not cause haemodynamic sequelae, it is none the less undesirable. This risk could be minimised by modifying our delivery system such that the fibre/catheter device is advanced into the coronary circulation without the fibre protruding from the catheter tip. The fibre tip could then be pushed out of the catheter tip once the catheter has been manipulated to the target lesion.

Fibre fracture and catheter damage occurred only in the region of the balloon, and only in those catheters in which the "through" and inflation lumens lay side by side, and were immediately recognisable by the failure of the balloon to inflate. But under these circumstances the catheter could be withdrawn without complication.

Percutaneous transluminal delivery of argon laser energy to the canine coronary circulation has been studied by others when a bare 200 μm core diameter fibre was used to deliver single 1 J or 2 J laser pulses to different coronary arterial sites; in nine arteries in five dogs laser perforation occurred in five and mechanical perforation in one.[10] In a similar study with a bare 400 μm core fibre and single laser pulses of 28 to 80 J at coronary sites in four dogs, immediate laser perforation occurred in all four.[11] In similar work on canine intracoronary thrombus, single pulses of 3 to 30 J caused laser perforation in seven out of nine dogs and recanalisation in one.[12] In these studies not only were the fibres of larger diameter than those used in our study (making them less flexible), but the fibres were not within a balloon angioplasty catheter. These factors, together with the higher delivered energies, would explain the high perforation rates at energies that were consistent with the perforation thresholds that we found. Also in the previous studies none of the dogs were recovered, so late follow up repeat angiography of previously lasered canine coronary arteries was impossible.

The delivery of laser energy has been studied in human peripheral[13-15] and coronary[16 17] circulations. A bare fibre with an olive-shaped metal tip was used for percutaneous intracoronary delivery[18-20] and in 14 cases there was one laser perforation and three myocardial infarctions. There are several potential dangers of laser angioplasty—acute vessel perforation, toxic byproducts of photovaporisation,[21] distal embolisation,[22 23] and delayed effects such as subsequent stenosis or aneurysm formation[24] but acute vessel perforation is the most important.

The risk of vessel perforation can be reduced by (*a*) selective enhancement of laser light absorption by atheroma (as opposed to that of the normal arterial wall) by using differential optical absorption peaks that are either naturally[25] or induced by photosensitisers,[26 27] (*b*) keeping the fibre central within the vessel lumen in order to reduce contact between fibre tip and arterial wall,[23] (*c*) modifying the fibre tip,[28 29] and delivering laser pulses of short duration that penetrate only a fraction of a millimetre into the target tissue. This may enable the operator to "nibble" away the atheroma gradually, while checking progress angiographically between laser pulses. Very short laser pulses (of nanosecond duration) limit the subjacent thermal damage, particularly if they are at the high peak powers obtainable from pulsed ultraviolet excimer lasers.[30 31] We have previously reported an in vitro dose-response relation between laser energy input and tissue penetration in normal and atheromatous human postmortem arterial wall.[7] This described a range of energy characteristics which, if applied to delivery of laser energy from the fibre tip in contact with and at right angles to the tissue, would not produce penetration further than 0·2–1·0 mm. The design of the present study is based on the energy characteristics of the argon laser established by that study. In the present study we used pulse energies which in vitro did not penetrate further than 1 mm into the target tissue, per J of argon energy delivered, and which were thought to be appropriate for "nibbling" away of atheroma.

We have now established in vivo the short term and long term angiographic effects of such amounts of argon laser energy and we know the amount that can safely be delivered to one site in the normal canine coronary circulation. If this cautious approach (that of "nibbling" away a millimetre of atheroma at a time without exceeding the maximum safe dose for normal arterial wall) is used clinically it may reduce the risk of acute laser perforation. The limitation of the system we have described is that the recanalised lumen that it creates is liable to be too small for physiological blood flow. But creation of even a tiny lumen may enable operators subsequently to cross those lesions which hitherto they had been unable to cross with the guide wire and balloon alone. Modified fibre tips make this appear feasible in the peripheral circulation[15 32]; however, further development is necessary before it can safely be applied to the coronary circulation.

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Patterns of diastolic dysfunction in left ventricular hypertrophy

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SUMMARY The relative sensitivities of and interrelations between different measurements of diastolic function were studied in 50 patients with left ventricular hypertrophy diagnosed on anatomical grounds. Isovolumic relaxation time, the interval from minimum cavity dimension to mitral valve opening and relative dimension increase during this period, and the peak rate of dimension increase and wall thinning during rapid ventricular filling were measured by digitised M mode echocardiography. The relative heights of peak early diastolic and atrial velocities (a/E) and the time for decline of early diastolic velocity to half its peak value (velocity half time) were measured on continuous wave and pulsed Doppler and the relative height of the "a" wave was measured by apexcardiogram. All sets of values except those of the interval from minimum dimension to mitral opening were unimodally distributed, and all differed significantly from those in 20 age matched controls. The relative height of the "a" wave on the apexcardiogram (90% values were abnormal) was the most sensitive method of studying left ventricular diastolic function and peak rate of dimension increase was the least sensitive. Though none of the correlations was high, there were individual associations between peak rate of dimension increase, a/E, peak wall thinning rate, and velocity half time, and independently between delay in mitral valve opening and dimension change during this period. Other values seemed to be independent of one another, suggesting a different physiological basis.

It is concluded that these various abnormal values do not reflect a single underlying disturbance of diastolic function. There are at least four possible discrete abnormalities: prolongation of isovolumic relaxation; incoordination during isovolumic relaxation; reduced rate of rapid filling; and an increase in the relative amplitude of the "a" wave probably caused by increased passive stiffness. These may be present singly or in combination in any patient.

Left ventricular diastolic function may be abnormal in various cardiac conditions including coronary artery disease and hypertrophy.[1-3] These diastolic abnormalities may be associated with limitation of exercise tolerance, added heart sounds, and evidence of increased atrial contraction. They have been detected by an increasing number of invasive and non-invasive methods during isovolumic relaxation, rapid ventricular filling, diastasis, and left atrial systole.[4-8] It is still not clear whether these all reflect, to a different extent, a single disturbance of diastole or whether there is more than one independent abnormality. We examined correlations between the results of several of these investigations in an homogeneous group of patients with left ventricular hypertrophy to determine the extent to which these different measurements are interrelated. In this way we hoped to provide a framework in which this growing body of information might be assimilated, and possibly to shed light on the nature of the underlying disturbances of diastole.

Patients and methods

STUDY POPULATION

An M mode echocardiogram, apexcardiogram, and Doppler echocardiograms were recorded in 50 patients with left ventricular hypertrophy. We selected patients in sinus rhythm in whom the left ventricular mass exceeded the normal 95% confidence interval. Patients were excluded if there

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was clinical evidence of coronary artery disease, mitral valve disease, valve regurgitation severe enough to increase cavity size, or evidence of regional abnormalities of wall motion on cross sectional echocardiography. The group with left ventricular hypertrophy was made up of 20 patients with hypertrophic cardiomyopathy, 24 with valvar or subvalvar aortic stenosis, and six with systemic hypertension. There were 27 male patients and 23 female patients, aged 12 to 74 years (mean 53).

Twenty subjects (11 male and nine female, aged 14–71 years) without heart disease underwent a similar cardiac investigation and served as normal controls.

M MODE ECHOCARDIOGRAM

The patients were studied in the partial left lateral position. The examination was completed in 10 to 15 minutes, during which time there was no obvious change in haemodynamic state. Echocardiograms were recorded with simultaneous phonocardiograms and electrocardiograms at a paper speed of 10 cm/s. A left ventricular echocardiogram at the level of the tips of the mitral valve (to define onset of cusp opening) showing clear continuous echoes from both the septum and posterior wall was used for further analysis (fig 1). The thickness of the septum and posterior wall was measured (cm) at end diastole (Q wave) by the leading edge method. The timing of aortic valve closure was taken as the onset of the first high frequency vibration of the aortic second heart sound and isovolumic relaxation as the interval between this and the initial separation of the mitral valve leaflets. The interval from minimum cavity dimension to mitral valve opening was measured (ms) and the increase in transverse cavity dimension during that period was expressed as a percentage of the total dimension change during the cardiac cycle.

Echocardiograms were digitised[6] by a Summagraphics digitiser and a Prime computer system. We

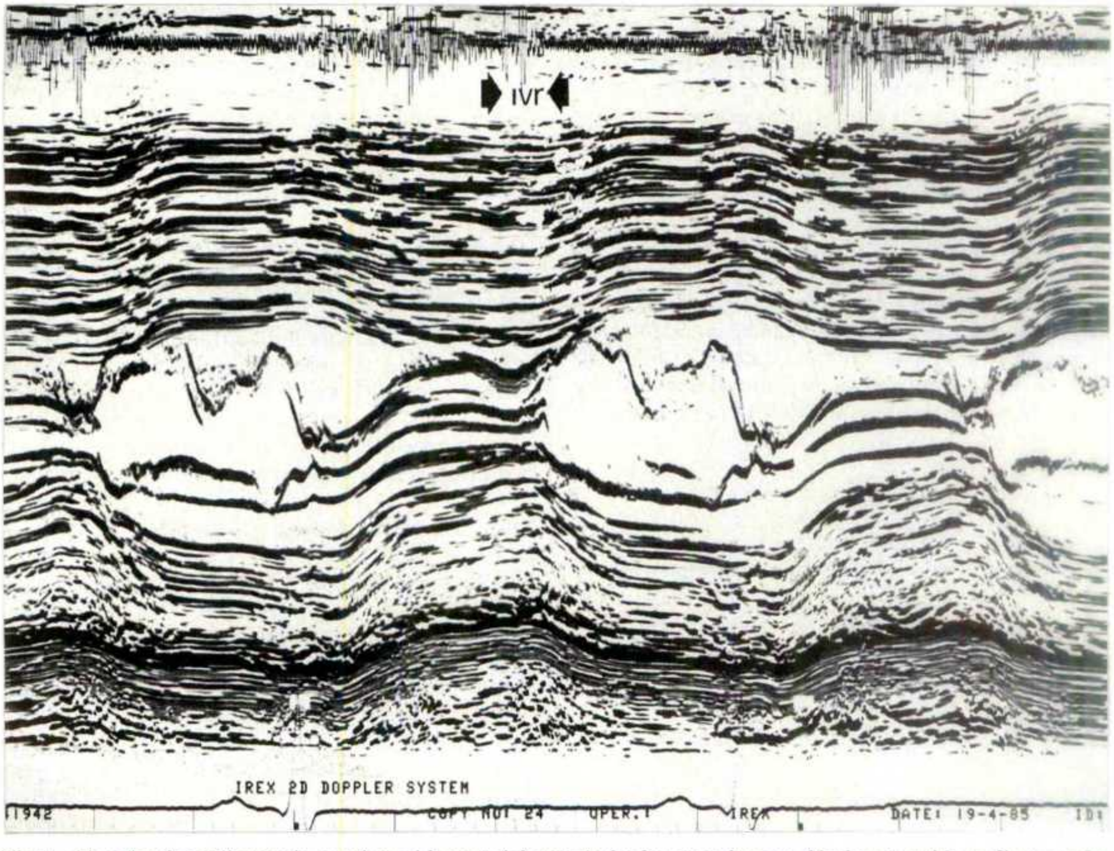

Fig 1 *M mode echocardiogram in a patient with severe left ventricular hypertrophy caused by hypertrophic cardiomyopathy. Isovolumic relaxation time (ivr) is prolonged (95 ms) but there is only minor delay in mitral valve opening relative to minimum cavity dimension without appreciable outward wall motion. Both the peak rate of dimension increase and posterior wall thinning are reduced.*

measured the peak rates (cm/s) of increase in dimension and posterior wall thinning during early diastole from the records.

APEXCARDIOGRAM

The apexcardiogram was recorded from the point of maximum cardiac impulse with the patient in the partial left lateral position. A transducer funnel that enclosed the impulse was selected (2·5 or 3 cm). The system had a time constant of 4 s with a lower frequency limit of 0·05 Hz. We calculated the ratio of the height of the A wave to the total deflection EO, (A/EO) from a mean of three cardiac cycles (fig 2).

DOPPLER ULTRASOUND

After a cross sectional echocardiographic study a continuous wave dual crystal Doppler transducer was placed at the point of maximum cardiac displacement. A 2 MHz transducer with either Doptek or Vingmed equipment interfaced with Irex spectral analysis was used. In addition, duplex scanning with pulsed Doppler ultrasound (Irex system III) was used in 20 patients with the sample gate placed just within the left ventricle. By inspection of the visual display and with the guidance of the audio signal, the angulation of the transducer was altered until the highest peaks of flow velocities in early and late diastole and the best possible graphic quality of the Doppler waveforms were obtained. Doppler signals were analysed by electronic fast Fourier transformation with sampling at 5 ms intervals and signal division into 128 frequency bins.

The following measurements were made on three cardiac cycles: the ratio of the peak height of the early diastolic (E) and atrial (a) waves (Doppler a/E) and the time taken for the peak early mitral flow velocity to decay by 50%; this is not equivalent to "pressure half time" because in contrast with the stenotic atrioventricular valve the decline in flow velocity across a normal valve is not exponential and during the phase of deceleration the pressure gradient is likely to be reversed. The measurement has therefore been referred to as a velocity half time.

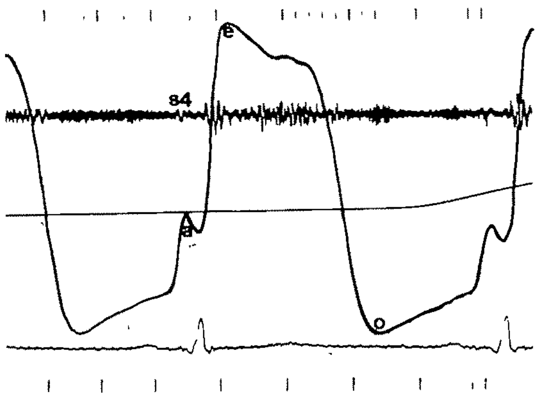

Fig 2 *Apexcardiogram in the same patient as fig 1 showing a markedly accentuated "a" wave coincidental with the phonocardiographic fourth heart sound (s4).*

STATISTICAL METHODS

Values are quoted as mean (1 SD). Student's *t* test (unpaired) was used to test differences between normally distributed variables and the Mann-Whitney U test between variables with a skewed distribution. The relation between continuously distributed variables was measured by Pearson's correlation coefficient (r). Fisher's exact probability test was used to test the power of association and the Kolmogorov-Smirnov test to determine the nature of numerical distribution. Measurement reliability was tested by the random selection of 10 sets of records and repetition of the measurements without prior knowledge of the previous results. Retest reliability coefficients were calculated; we assumed an ideal value of unity. The retest reliability coefficients for the Doppler ultrasound, apexcardiogram, and M mode echocardiogram measurements were adequate and exceeded 0·9 in each case. Individual values were taken to be abnormal if they lay outside the 99% confidence interval of the normal group.

Results

MEAN CAVITY DIMENSION AND WALL THICKNESS

By definition, patients with left ventricular hypertrophy had a thicker posterior wall and septum than normal controls (1·4 (0·3) and 1·8 (0·5) cm *vs* 0·8 (0·1) and 0·9 (0·2) cm respectively). By definition, also, cavity dimensions in patients with left ventricular hypertrophy did not differ significantly from normal.

DIASTOLIC FUNCTION BY DOPPLER ULTRASOUND (TABLE 1)

The Doppler ratios of a/E measured by continuous (0·9 (0·46)) and pulsed methods (0·87 (0·45)) had similar mean values and a correlation coefficient of r = 0·94 (p < 0·001). Velocity half times measurement by continuous (119 (50)ms) and pulsed Doppler (120 (51)ms) were similar with a correlation coefficient of r = 0·93 (p < 0·001). Because there were no significant differences between any individual subgroups with left ventricular hypertrophy, all 50 patients were considered together. As expected they differed significantly from the normal group: the Doppler ratio a/E was greater (p < 0·001) with 15 (30%) outside the normal 99% confidence interval and the velocity half time was reduced

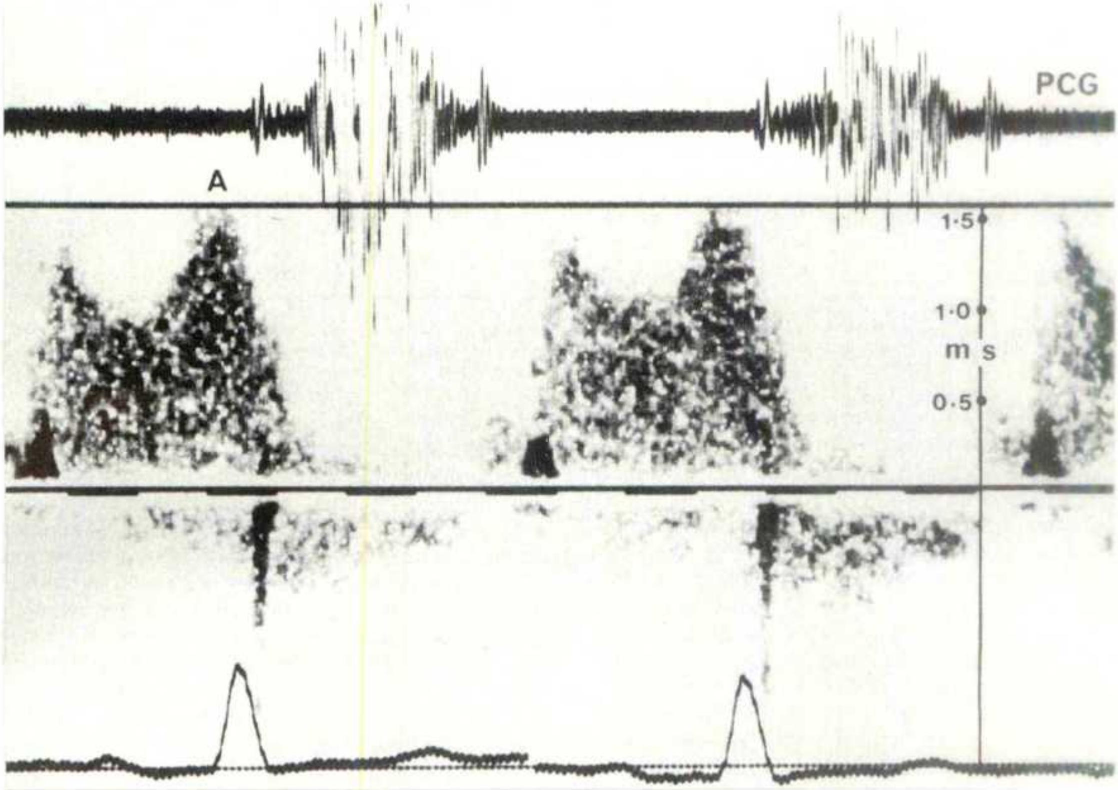

Fig 3 *Apical continuous wave Doppler study showing a reduced velocity half time and a dominant A wave in a patient with aortic stenosis.*

($p < 0{\cdot}001$) with only 17 patients within the normal range (table 1).

DIASTOLIC FUNCTION BY DIGITISED M MODE ECHOCARDIOGRAPHY

Mean isovolumic relaxation time was longer in patients with left ventricular hypertrophy than in normal controls. Twenty one (42%) patients had values above the upper 99% confidence interval for normal and six had values below the lower limit. In patients with left ventricular hypertrophy mitral valve opening was delayed by 77 (45) ms relative to minimum dimension (normal 10 (3), $p < 0{\cdot}001$), with two having values below and 40 values above the normal 99% confidence interval. In patients with left ventricular hypertrophy the change in dimension before mitral valve opening was 20(19)% compared with the normal of 0(3)%, with one patient having values below and 32 values above the normal 99% confidence interval. The mean values for the peak rate of dimension increase and wall thinning were both less than normal ($p < 0{\cdot}001$) with 15 and 24 patients respectively having values below the normal range.

DIASTOLIC FUNCTION BY APEXCARDIOGRAPHY

Only five patients with left ventricular hypertrophy had a normal A/EO and in this group the mean value was greater than normal ($p < 0{\cdot}001$).

Table 1 *Comparison of diastolic function in normal controls and patients with left ventricular hypertrophy*

	Normal	*Left ventricular hypertrophy*
No	20	50
a/E (%)	0·52 (0·12)	0·71 (0·4)
Velocity half time (ms)	62 (14)	126 (38)
A/EO (%)	0·07 (0·02)	0·26 (0·02)
Isovolumic relaxation time (ms)	57 (8)	90 (38)
Minimum dimension (ms) to MVO	10 (3)	77 (45)
Dimension change before MVO (%)	0 (3)	20 (19)
Peak rate (cm/s) of dimension increase	14 (3)	9·7 (3·6)
Peak rate (cm/s) of wall thinning	9 (2)	5·4 (2·4)

a/E, Doppler ratio of "a" to E waves; MVO, mitral valve opening; A/EO, apexcardiographic relative height of "a" wave. Values are mean (1 SD).

Table 2 *Distribution of values outside the normal 99% confidence interval*

	Number of values greater than normal 99% confidence interval								
	Total	*a/E*	*VHT*	*A/EO*	*IVR*	*PRF*	*PRT*	*MDMVO*	*DCMVO*
a/E	15 (30%)		11	12	5	8*	10	13	11
VHT	33 (66%)	11		30	21	13*	20	25	22
A/EO	45 (90%)	12	30		21	13	20	33	30
IVR	21 (42%)	5	13	21		6	9	19	7
PRF	15 (30%)	8	12	12	6		1	8	7
PRT	24 (48%)	10	17	20	9	10*		19	17
MDMVO	40 (80%)	13	25	33	19	8	19		34*
DCMVO	43 (86%)	11	22	30	17	7	17	34*	

*$p < 0{\cdot}01$ Fisher exact probability test

VHT, velocity half time; IVR, isovolumic relaxation, PRF, peak rate of dimension increase; PRT, peak rate of wall thinning; MDMVO, minimum dimension to mitral valve opening, DCMVO, dimension change before mitral valve opening.

CORRELATION OF METHODS IN DETECTING ABNORMAL DIASTOLIC FUNCTION

If two tests are totally independent, the results of the first will be of no value in identifying patients with an abnormal result in the second. If, on the other hand, there is dependence between the two, the second test will be positive more often in patients in whom the first test was abnormal. Table 2 gives the information used to assess the degree of dependence in this way. The total number of patients in whom values were outside the normal 99% confidence interval for each test are given in the left hand column. The remaining columns show the frequency with which the other tests were positive in patients with positive results in the first test. There were correlations between a/E and peak rate of dimension increase, between velocity half time and peak rate of dimension increase, and between peak rate of dimension increase and peak thinning rate. A separate relation was noted between delay in mitral valve opening with respect to minimum dimension and the dimension change during that period (all $p < 0{\cdot}01$ by Fisher's exact probability test). For the remaining tests positive results in the second test were unrelated to positive results in the first test.

When the results in individual patients were examined the conclusion was similar. The Doppler a/E ratio correlated with velocity half time ($r = 0{\cdot}50$, $p < 0{\cdot}001$) and with peak rate of dimension increase ($r = 0{\cdot}41, p < 0{\cdot}01$). Velocity half time was related to peak rate of dimension increase ($r = 0{\cdot}51, p < 0{\cdot}001$) and posterior wall thinning ($r = 0{\cdot}44$, $p < 0{\cdot}01$). Correlations obtained by pulsed and continuous Doppler did not differ significantly. Minimum dimension to mitral valve opening and dimension change during this period were correlated significantly with each other ($r = 0{\cdot}7, p < 0{\cdot}001$) but not with any other measurements. There were no other significant correlations except an expected one between peak rate of dimension increase and wall thinning ($r = 0{\cdot}71$, $p < 0{\cdot}001$). In the population with left ventricular hypertrophy all results were unimodally distributed, except those measurements of dimension change before mitral valve opening, which showed peaks at 15% and 50% total dimension change respectively. The former is within the normal 99% confidence interval and the latter outside it. There was no predominance of any patient group in either peak, however.

Discussion

Diastolic left ventricular function is often abnormal in patients with left ventricular hypertrophy,[39] and more abnormalities are reported as new methods are described for its study. It is not clear, however, how all these measurements, often referred to as "parameters" of diastolic function, relate to one

Table 3 *Correlation between measurements of diastolic function in patients with left ventricular hypertrophy*

	a/E (CW)	*VHT (CW)*	*A/EO*	*IVR*	*PRF*	*PRT*	*MDMVO*	*DCMVO*
VHT (CW)	0·5*		0·16	0·02	0·5*	0·44*	0·03	0·01
a/E (CW)		0·5*	0·37†	0·17	0·4*	0·13	0·04	0·08
VHT (PW)	0·87‡	0·94‡	0·27	0·105	0·58*	0·51*	0·2	0·2
a/E (PW)	0·94‡	0·83‡	0·34	0·21	0·55*	0·3	0·01	0·1
A/EO	0·37†	0·16		0·05	0·01	0·01	0·03	0·1

CW and PW represent continuous and pulsed wave Doppler recordings.
Significance of r value: *$p < 0{\cdot}01$, †$p < 0{\cdot}05$; ‡$p < 0{\cdot}001$
See footnote to table 2 for abbreviations.

another. One view is that they all reflect, to a greater or lesser extent, some single underlying disturbance, such as "impaired relaxation"[10] or "reduced compliance".[11] If so, the various methods can only diverge in individual patients because of incidental factors such as their relative indirectness or simply random error. An alternative view is that two or more discrete disturbances of diastolic function exist, whose extent can vary independently between patients. We aimed to study this problem by making a series of measurements of diastolic left ventricular function in a homogeneous group of patients with left ventricular hypertrophy confirmed by well defined anatomical criteria. The majority had outflow tract obstruction or hypertrophic cardiomyopathy. The methods were designed to cover all aspects of diastole from isovolumic relaxation to atrial systole, and we were interested not only in their relative sensitivity in detecting any abnormality, but also in their distribution and the extent to which their results were independent of one another.

Our results confirm that all the methods we used frequently gave values outside the 99% confidence interval of an age matched normal population. We chose 99% rather than 95% intervals because our normal population was not large enough to allow us to derive the relation between these normal intervals and age, and because we used them to identify abnormal values in individual patients.[12 13] Some methods gave abnormal values much more often than others. Those that were most often abnormal were an increase in the relative height of the "a" wave on the apexcardiogram and delay in mitral valve opening with respect to minimum cavity dimension. The relative height of the "a" wave on the Doppler echocardiogram (a/E) and peak rate of dimension increase on the M mode echocardiogram were abnormal least often. Intermediate were the duration of isovolumic relaxation, the rate of velocity decline at the end of the rapid phase of left ventricular filling, and peak rate of thinning of the posterior left ventricular wall.

Although values for these different measurements did not correlate closely in individual patients, there were significant associations. Thus a reduced rate of dimension increase was much commoner in patients with a prolonged flow velocity decline than in those in whom it was normal; a/E ratio and peak rate of dimension increase were similarly associated. This suggests that these three quantities were not independent of one another. In the same way, the delay in mitral valve opening with respect to minimum dimension was independently related to the extent of left ventricular dimension increase during the same period, but not with isovolumic relaxation time itself. Indeed, we could not demonstrate any association between isovolumic relaxation time or the relative height of the "a" wave on the apexcardiogram and any other of the variables that we investigated. The measurements themselves were all internally consistent, and values often departed considerably from normal in patients with left ventricular hypertrophy. We are not therefore inclined to ascribe this independence simply to extensive noise or physiological variation confounding our attempts to determine the extent of a single disturbance, but rather we consider it provides evidence that there is more than one discrete determinant of diastolic function.

Most of the measurements we made were unimodally distributed throughout the patient population. Those of dimension increase before mitral valve opening were exceptional in falling into two groups, one with values only slightly higher than normal and the other in which they were considerably more disturbed. An increase in cavity dimension during isovolumic relaxation must represent a change in ventricular cavity shape and not the effect of filling, so both it, and also the delay in mitral valve opening with which it is associated, are likely to be the result of incoordination during early diastole. Although its mechanism is not clear, it appears that partial forms of this aspect of incoordination do not exist, and that it is either present in fully developed form or absent altogether. By contrast, prolongation of isovolumic relaxation time not only behaved independently of these other two measures but also was continuously distributed, and so is likely to have some other mechanism. This distinction has practical importance, since the interval from minimum dimension to mitral valve opening has been used as a measure of isovolumic relaxation time, and has even been termed "isovolumic relaxation time index".[14] Our results not only demonstrate that the two measurements behave independently in patients with left ventricular hypertrophy in whom this index has been used, but suggest that they may even have different underlying mechanisms.

The basis of the apexcardiogram during diastole is known to depend mainly on left ventricular pressure.[15] An increase in the relative height of the "a" wave is thus likely to reflect the combined effect of a larger atrial stroke volume and a stiffer left ventricular cavity. It was thus interesting that this relatively direct measurement proved so much more sensitive than the Doppler determination of relative blood velocity at the same time. This discrepancy emphasizes how little is known of what determines atrial flow rate. It is more a manifestation of atrial systolic rather than ventricular diastolic function. Flow velocity presumably increases only when some abnormal ventricular diastolic property acts as an increase in atrial afterload, though how a change in atrial loading conditions affects its systolic function is not well understood. Our results make it unlikely that this intermediate factor is simply an increase in ventricular end diastolic pressure. Of the measurements with which it was interrelated, two—flow velocity decline and peak rate of dimension increase—were both measures of rapid filling, and on this basis it may be that the a/E ratio depends more on a low early diastolic flow velocity, with the increase during atrial systole being merely compensatory.

Ventricular loading conditions greatly affect measurements of diastolic function, particularly relaxation.[16] The question thus arises as to whether this load dependence could cause the discrepancies between measurements in individual patients. Though load dependence may modify the rate of relaxation, if relaxation rate itself is the only determinant of diastolic function, variation in loading could not explain discrepancies between methods unless it was actually altering at the time that measurements were made. Changes in loading can also alter individual and potentially independent measurements by a variety of other mechanisms. Isovolumic relaxation time shortens when left atrial pressure rises, though it is little affected by aortic pressure.[17] Ventricular filling rate increases when atrioventricular pressure gradient rises,[10] and an increase in left atrial pressure increases the prominence of the "a" wave on the apexcardiogram.[15] Had loading conditions been a significant source of variance, therefore, correlation would have been expected between these three variables. Its conspicuous absence suggests that other factors must be involved.

Several conclusions can be drawn from these results about diastolic abnormalities of the left ventricle occurring in uncomplicated hypertrophy. In having two subgroups, incoordination differs fundamentally from the remainder of the variables which were continuously distributed. The overall sensitivity of the different measurements in detecting abnormalities varied widely, ranging from less than 50 to more than 90%. Finally, individual measurements appeared to associate themselves into four sets giving results that were independent of one another. Even at the present stage, therefore, our findings are incompatible with the original premise that all diastolic abnormalities reflect, to some degree, the severity of a single, scalar disturbance of left ventricular function, whatever its nature. Rather, they suggest the existence of a series of independent disturbances, present to varying degrees in individual patients. We suggest that they might be classified as follows: type 1 presenting as prolongation of isovolumic relaxation time, which, in the absence of abnormal loading conditions, is likely to be due to a reduction in the rate of ventricular pressure fall. Incoordinate wall motion or stress reduction during isovolumic relaxation is responsible for type 2 abnormalities, while type 3 disturbances reflect a reduced rate of rapid filling. Type 4, here represented by a relative increase in the height of the "a" wave on the apexcardiogram, is probably caused by increased passive stiffness of the ventricular cavity.[18] Other abnormalities certainly exist within each group, and this classification allows for further independent mechanisms to be described. Future work should therefore be directed towards defining other abnormalities in greater detail and understanding when and why they occur.

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Haemodynamic effects of short term intravenous amiodarone for hypertrophic cardiomyopathy

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SUMMARY The haemodynamic effects of an intravenous amiodarone infusion (5 mg/kg for 10 minutes) were measured in ten patients with hypertrophic cardiomyopathy (two with a left ventricular outflow gradient at rest) five, 15, and 30 minutes after drug administration. Mean (SD) pulmonary capillary wedge pressure rose significantly at five and 15 minutes (from 12·3 (6·2) mm Hg to 17·6 (9·2) and to 16·2 (8·6)) with a subsequent tendency to fall to control values at 30 minutes. Mean right atrial and right ventricular end diastolic pressures increased from 3·6 (1·8) mm Hg to 7·3 (3·1) and from 6·3 (2·4) to 9·8 (3·2) mm Hg respectively at 30 minutes. The increase in filling pressures was paralleled by a decrease of left ventricular max dP/dt from 1522 (414) to 1372 (327) to 1316 (338) and to 1326 (379) five, 15, and 30 minutes after infusion. Despite this slight negative inotropic effect, cardiac index and stroke volume index were unchanged or slightly increased, possibly because of the decrease in systemic vascular resistance (from 1326 (330) dyn s cm^{-5}/m^2 to 1152 (285)). In both patients with outflow gradient the pressure gradient at rest decreased (from 110 to 65 and from 85 to 65 mm Hg) through a reduction of left ventricular systolic pressure.

Thus short term intravenous infusion of amiodarone is safe in patients with hypertrophic cardiomyopathy. The main changes were a mild depression of ventricular contractility, which was well tolerated and adequately compensated for by a decrease in afterload.

Over the past few years amiodarone has become widely accepted as a first line management of arrhythmias in patients with hypertrophic cardiomyopathy.[1-3] Its haemodynamic action after intravenous administration has been extensively studied in patients with coronary artery disease[4-6] but no data are available on the short term effects in hypertrophic cardiomyopathy. Because the pathophysiology of hypertrophic cardiomyopathy is unique, the haemodynamic effects seen in other cardiac diseases may not necessarily be found in this disorder. For this reason we studied the haemodynamic effects of intravenous amiodarone in 10 patients with hypertrophic cardiomyopathy.

Patients and methods

PATIENTS

Ten patients (eight men and two women, aged 36 (13) years (mean (SD)) (range 19 to 55 years)) were studied after giving their informed consent. They were the first ten patients referred to this hospital who were not already taking oral amiodarone when the study was planned. Only two patients had a left ventricular outflow gradient (110 and 85 mm Hg). Initial evaluation included 48 hours electrocardiographic recording (Holter), which showed paroxysmal atrial fibrillation or supraventricular tachycardia or both in six patients and runs of ventricular tachycardia in four.

Table 1 summarises patient characteristics, predominant symptoms, New York Heart Association functional class, distribution and extent of left ventricular hypertrophy, and 48 hour Holter data. The distribution of left ventricular hypertrophy was classified according to Maron *et al*[7] based on cross sectional echocardiographic findings. The presence or absence of systolic anterior movement of the mitral valve on the echocardiogram was noted.

CATHETERISATION PROCEDURES

All patients had standard right and left sided cardiac

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Table 1 *Patients' characteristics*

Patient	*Age (yr)*	*Sex*	*Symptoms and NYHA class*	*Distribution of LVH**	*Echo thickness (mm)*			*Main findings on 48 h Holter*
					IVS	*LVPW*	*SAM*	
1	55	M	No, I	Type III	22	21	No	PSVT, VE Lown III
2	43	F	Dyspnoea, II	Concentric	23	15	Yes	PSVT, VE Lown III
3	23	M	Palpitation, II	Type II	20	11	No	Unsustained VT, PAF
4	51	M	Dyspnoea, III	Type III	35	11	Yes	PSVT
5	20	M	No, I	Type III	28	16	No	Unsustained VT
6	40	F	Palpitation, II	Type IV	12	11	Yes	PSVT
7	34	M	Palpitation, II	Type II	18	13	No	PSVT, VE Lown III
8	19	M	Palpitation, II	Type III	34	10	Yes	PAF
9	33	M	Dyspnoea, II	Type III	21	14	Yes	Unsustained VT
10	43	M	Palpitation, II	Type I	18	12	No	Unsustained VT

LVH, left ventricular hypertrophy; IVS, interventricular septum; LVPW, left ventricular posterior wall, SAM, systolic anterior movement; PSVT, paroxysmal supraventricular tachycardia; VE, ventricular extrasystoles, VT, ventricular tachycardia; PAF, paroxysmal atrial fibrillation.

*According to Maron *et al.*[7]

catheterisation without premedication after an overnight fast. A 7F Swan-Ganz thermodilution catheter was inserted percutaneously from the right femoral vein with its tip in a pulmonary artery and the proximal lumen in the right atrium. A 8F double lumen micromanometer tip Millar catheter was advanced from the right femoral artery in an arterial sheath to the body of the left ventricle. We ensured that entrapment, spurious gradient, or arrhythmias would not occur. Systemic arterial pressure was monitored from the side arm of the arterial sheath (8F) or from a second arterial line if the quality of the pressure wave from the sheath was unsatisfactory.

Cardiac output was measured in triplicate by the thermodilution technique; heart rate (mean of six beats) and rhythm were recorded by the electrocardiogram.

MEASUREMENTS

Reference 0 for pressure measurements was set at mid-chest level. The micromanometer was calibrated with the fluid filled system of the lumen of the Millar catheter itself. All pressure measurements were the mean of 5–10 consecutive beats. When we recorded pressure-derived contractility and relaxation indexes, the patients were asked to hold their breath at mid-inspiration. We calculated the following variables from pressure and flow measurements: systemic vascular resistance (mean blood pressure/cardiac output); pulmonary vascular resistance (mean pulmonary artery − pulmonary capillary wedge pressure/cardiac output); cardiac index (cardiac output/body surface area); stroke volume (cardiac output/heart rate); peak positive left ventricular pressure first time derivative (max dP/dt); peak negative dP/dt; and time constant of left ventricular pressure fall after the peak negative dP/dt (T). Left ventricular and pulmonary capillary wedge pressures were recorded at a paper speed of 200 mm/s and the left ventricular pressure values taken at 10 ms intervals from the peak negative dP/dt to the end of isovolumetric diastole determined by the point at which left ventricular pressure crosses the wedge pressure tracing and these data were fitted by the method of least squares to the function $P = e^{At+B}$. The time constant T equals $1/-A$, where A is the slope of ln P plotted against time and expressed as s^{-1}.[8]

Study protocol

Twenty minutes were allowed for stabilisation before we took a complete set of baseline measurements. Then amiodarone (5 mg/kg body weight) was infused over ten minutes. We used the commercially available preparation (Cordarone) containing the diluent Tween 80. Haemodynamic measurements were repeated five, 15, and 30 minutes after the end of the injection. Cardiac output and the derived variables were only measured at 30 minutes.

Statistical evaluation

Statistical analysis was performed by Student's *t* test for paired data. A p value $< 0{\cdot}05$ was considered to be significant. Values are expressed as mean (1 SD).

Results

Table 2 shows individual and mean haemodynamic data. Figures 1, 2, and 3 show the individual changes in pulmonary capillary wedge pressure, left ventricular end diastolic pressure, max dP/dt, peak negative dP/dt, time constant T, cardiac index, stroke volume, and systemic vascular resistance. Five and 15 minutes after amiodarone pulmonary wedge pressure rose significantly whereas at 30 minutes there was tendency to return to control values (fig 1). In one of the two patients (fig 1) with a left ventricular outflow gradient, pulmonary capillary wedge pressure rose to 30 mm Hg at five and 15 minutes and returned to baseline value at 30 minutes in the absence of symptoms and clinical problems.

Table 2 *Mean haemodynamic data obtained at baseline and after amiodarone infusion*

		After amiodarone infusion		
	Baseline	*5 min*	*15 min*	*30 min*
HR (beats/min)	81·5(8.7)	83·3(6·4)	78·9(4·2)	79(3·3)
RAMP	3·6(1·8)			7·3(3·1)***
RVEDP	6·3(2·4)			9·8(3·2)**
PAP				
Systolic	32(13)	37(10·9)**	35·5(13·1)*	34·5(13·6)
Diastolic	15·7(7·3)	19·5(6·6)**	18·2(7·7)**	16·5(7)
Mean	18·5(9)	24·3(7·9)***	22·5(7·8)**	21·6(8·8)*
PCWP	12·3(6·2)	17·6(9·2)**	16·2(8·6)*	14·3(5·9)
LVSP	137(59)	129(46)	129(48)	130(44)
LVEDP	19·9(5·9)	22·4(6·3)	20·5(6·6)	20·3(6·4)
AoP				
Systolic	117(27)	116(26)	116(29)	119(25)
Diastolic	74(9)	69(11)*	71(12)	71(11)
Mean	87(15)	83(19)*	86(20)	86(17)
CI (l/min/m^2)	3(0·8)			3·3(0·6)
SVI (ml/m^2)	38(11)			41(8)
SVR (dyn s cm^{-5}/m^2)	1325(330)			1156(280)*
PVR (dyn s cm^{-5}/m^2)	107(78)			117(96)
Peak positive dP/dt (mm Hg/s)	1522(414)	1372(327)*	1316(338)**	1326(339)*
Peak negative dP/dt (mm Hg/s)	1340(428)	1272(345)	1298(351)	1359(378)
T (ms)	54·3(13·2)	64·6(17·4)*	57·2(14·7)	55·5(14·5)

Values are mean (SD) and pressures are mm Hg

HR, heart rate; RAMP, right atrial mean pressure, RVEDP, right ventricular end diastolic pressure, PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure (mean); LVSP, left ventricular systolic pressure, LVEDP, left ventricular end diastolic pressure, AoP, aortic pressure; CI, cardiac index; SVI, stroke volume index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance

T is the time constant of the fall in left ventricular pressure

*p < 0·05, **0·01, ***0·001 (versus baseline).

A table of results for individual patients is available from the authors.

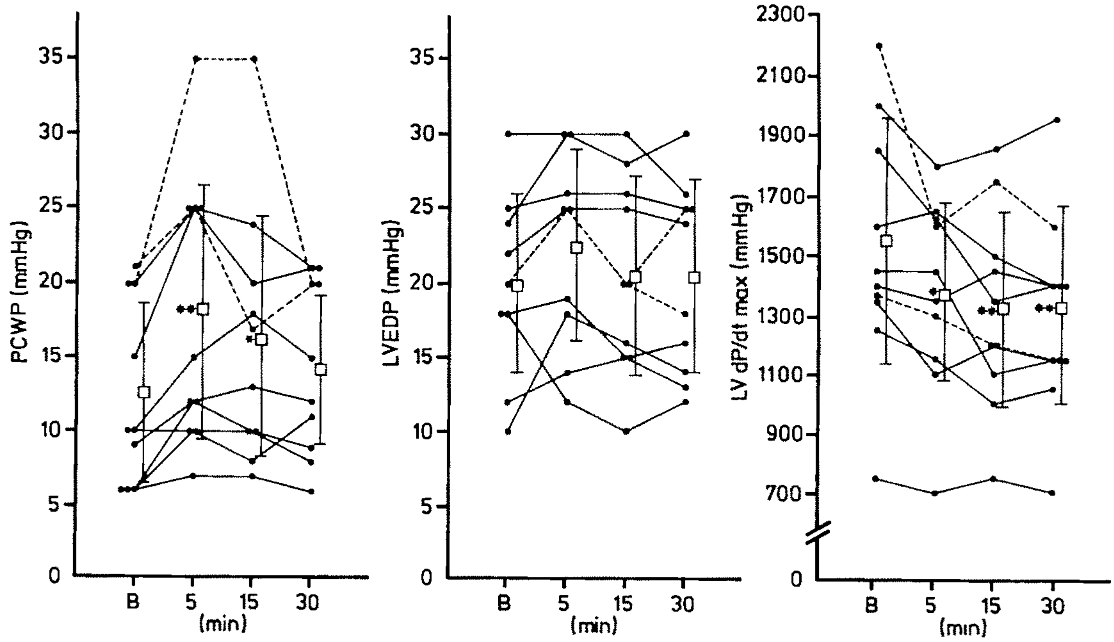

Fig 1 *Effects of amiodarone infusion on mean pulmonary capillary wedge pressure (PCWP), left ventricular end diastolic pressure (LVEDP), and left ventricular (LV) max dP/dt. Individual and mean (SD) values are shown at baseline (B) and five, 15, and 30 minutes after amiodarone infusion. The dotted lines identify the two patients with left ventricular outflow gradient at rest. *p < 0·05 vs baseline value; **p < 0·01 vs baseline value.*

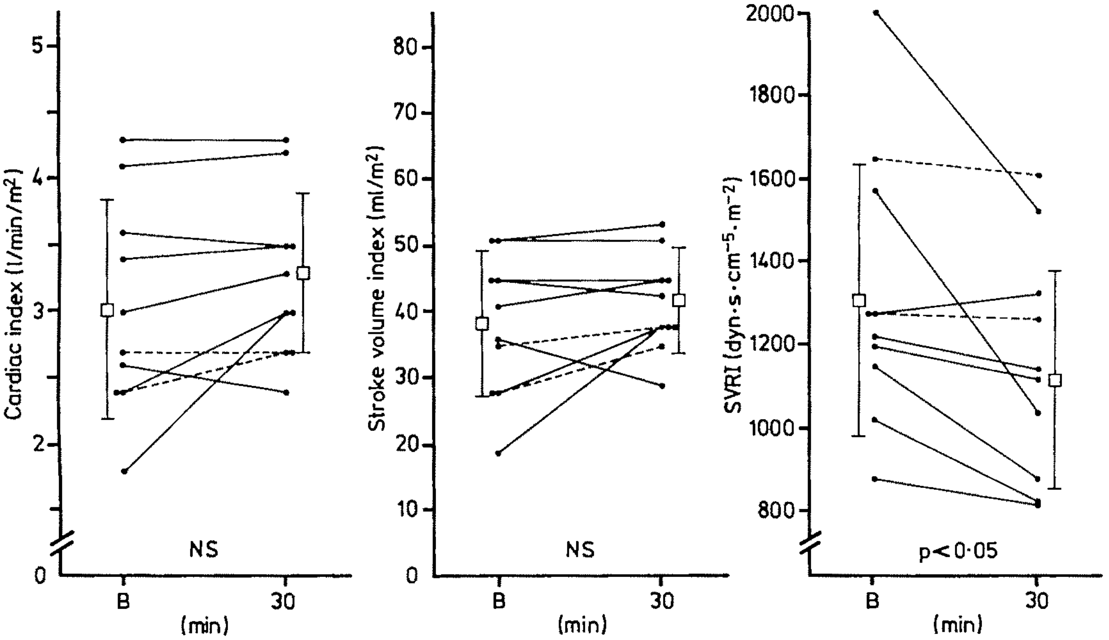

Fig 2 *Effects of amiodarone infusion on cardiac index, stroke volume index, and systemic vascular resistance index (SVRI). Individual and mean (SD) values are shown at baseline (B) and 30 minutes after amiodarone infusion. The dotted lines identify the two patients with left ventricular outflow gradient at rest.*

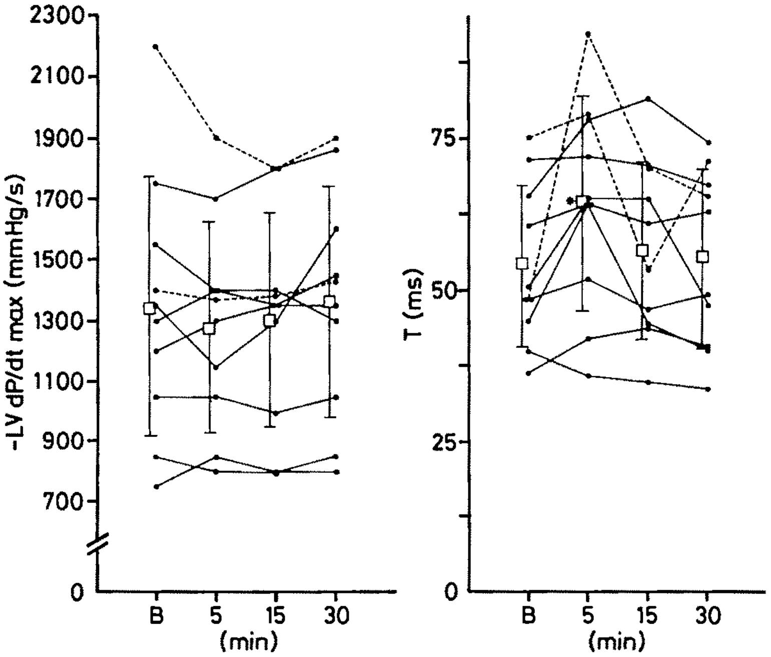

Fig 3 *Effects of amiodarone infusion on left ventricular peak negative dP/dt (− LV dP/dt max) and time constant (T) of the fall in left ventricular pressure. Individual and mean (SD) values are shown at baseline (B) and five, 15, and 30 minutes after amiodarone infusion. The dotted lines identify the two patients with left ventricular outflow gradient at rest.* *$p < 0{\cdot}05$ *vs baseline.*

There was a smaller and not statistically significant increase in left ventricular end diastolic pressure. The increase in pulmonary wedge pressure was paralleled by a decrease in max dP/dt that remained statistically significant at 30 minutes. These results are consistent with a slight negative inotropic action of amiodarone. The finding that cardiac index and stroke volume were unchanged or increased slightly at 30 minutes, however, may be the result of the decrease in peripheral resistance (fig 2). In fact mean systemic vascular resistance was significantly reduced at 30 minutes. In five patients there was a decrease while in the other five there was no change or a minimal reduction (fig 2). Heart rate did not change significantly at any time. Mean right atrial pressure and the right ventricular end diastolic pressure were also increased. The time constant T rose significantly at five minutes, indicating a transient reduction in relaxation.

Discussion

The management of cardiac arrhythmias is a major task in patients with hypertrophic cardiomyopathy. Oral treatment is the usual treatment but often intravenous administration may be required, for example in patients who are haemodynamically unstable during the arrhythmic phases or in between them, and in whom immediate interruption of the arrhythmia or its prevention is important.

Although amiodarone is an effective antiarrhythmic drug for patients with hypertrophic cardiomyopathy,[1-3] it may take several days to reach therapeutic concentrations in the blood and suppression of arrhythmia,[9-11] even with a large oral loading dose. Intravenous bolus injection of amiodarone has been demonstrated to be effective in controlling various supraventricular and ventricular arrhythmias.[12-14] Intravenous administration is usually followed by continuous infusion as a long term oral regimen is started. This approach shortens the loading period.

The effect of long term oral amiodarone on left ventricular function in hypertrophic cardiomyopathy has been reported recently.[15 16] Sugrue *et al* studied systolic and diastolic left ventricular function at rest with serial radionuclide angiograms and found that ejection fraction and left ventricular filling indices were not altered.[15] Paulus *et al* reported a negative effect on rest and exercise haemodynamic function with no effect on echocardiographic relaxation indices.[16] In that study the significant increase in left ventricular filling pressures at rest and the higher pulmonary capillary wedge pressures during exercise at identical workloads are consistent with a negative inotropic action of amiodarone

Information on the haemodynamic effects of intravenous amiodarone has been obtained from studies on normal volunteers[17 18] or patients with ischaemic heart disease[4 6 19] or depressed left ventricular function of different causes.[5 20] In these conditions intravenous amiodarone had both negative inotropic and peripheral vasodilatory effects. The consensus is, however, that the haemodynamic changes are a consequence of the combined effects of the drug and its diluent Tween 80. Sicart *et al* compared the effects of amiodarone with solvent and pure Tween 80.[17] They concluded that the early vasodilatation was primarily but not exclusively caused by Tween 80, while the later reduction in contractility was caused by amiodarone itself. The effects induced by the diluent lasted only up to four minutes. Bellotti *et al* infused amiodarone not dissolved in Tween 80 into patients with congestive heart failure caused by chronic Chagas's disease and found both a negative inotropic effect and a peripheral vasodilatation.[20]

In the previously reported studies amiodarone was injected at doses of 5–10 mg/kg over periods of 1–5 minutes. A more gradual intravenous administration of the drug has been advised to avoid the possible acute hypotension.[21] In the present study we increased the time of infusion to 10 minutes and started to measure the haemodynamic effect five minutes after the end of the infusion. The haemodynamic changes that we measured are therefore more likely to reflect the action of the drug alone.

In the present study the main effect of short term intravenous amiodarone was a mild depression of myocardial function. This was shown by an increase in right and left filling pressures and by a decrease in left ventricular max dP/dt. Simultaneous systemic vasodilatation, however, compensated for the effect on contractility and cardiac output was maintained. Despite the decrease in systemic vascular resistance, there was no reflex increase in heart rate. This finding can be explained by the drug's properties of non-competitive blockade of both α and β receptors.[22-24] Left ventricular dP/dt is load dependent, so the observed reduction in this variable could have been caused by a reduction in systemic vascular resistance itself, unassociated with any reflex adrenergic response. A true decrease in contractility is, however, a more likely explanation because max dP/dt also fell in those patients who did not show any reduction of systemic vascular resistance.

The two patients with left ventricular outflow gradient showed the same haemodynamic changes that were seen in the others: in both cases the gradient decreased because there was a moderate reduction of left ventricular systolic pressure.

The ability of amiodarone to reduce the afterload seemed to be most relevant in determining the behaviour of the stroke volume. When the patients who showed a decrease in afterload (as reflected by systemic resistance or by the left ventricular outflow gradient) are considered separately from those in whom the afterload did not change, it can be seen that max dP/dt, pulmonary capillary wedge pressure, and left ventricular end diastolic pressure changed in the same direction or did not differ significantly in the two subgroups, while stroke volume increased only in those patients who showed a decrease in afterload (fig 4). Since filling pressures also rose in these patients we believe that the reduction in afterload overcompensated for the reduction in contractility. This would imply an increase in left ventricular volumes.

We interpreted the increase in filling pressures as a negative inotropic effect of amiodarone. This finding could also be explained by a reduction in ventricular compliance. Amiodarone did not modify the peak negative dP/dt but it did significantly increase the time constant of left ventricular pressure fall (T) at five minutes, which indicates a reduction in relaxation (fig 3). This effect was transient and did not persist at 30 minutes when the simultaneous changes in stroke volume, systemic vascular resistance, contractility, and filling pressure were considered.

The results of the present study indicate that short term intravenous amiodarone may be given safely to patients with hypertrophic cardiomyopathy and that the main changes are a slight depression of cardiac function that is well tolerated and adequately compensated for by systemic vasodilatation. Transient reduction in compliance caused by impaired relaxation cannot be excluded. The patients did not report any subjective side effects.

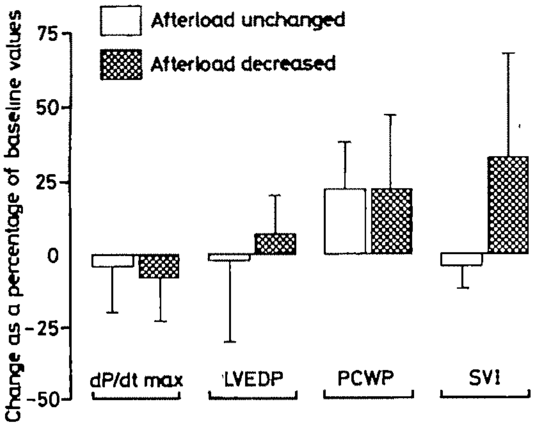

Fig 4 *Change (mean (SD)) in left ventricular dP/dt max, left ventricular end diastolic pressure (LVEDP), pulmonary capillary wedge pressure (PCWP), and stroke volume index (SVI) 30 minutes after amiodarone infusion as a percentage of baseline values. The patients are divided into two subgroups—those with minimal (≤5%) changes of systemic vascular resistance (that is afterload unchanged) and those with a reduction in systemic vascular resistance or in left ventricular aortic pressure gradient (that is afterload decreased).*

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Cryoablation of the accessory pathway in Wolff-Parkinson-White syndrome: initial results and long term follow up

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SUMMARY Cryoablation of the accessory pathway was used in the management of 20 patients with pre-excitation syndromes. All patients had presented with paroxysmal atrioventricular reentrant tachycardia; in addition, six had experienced atrial fibrillation. In 16 patients pre-excitation was overt and in four the accessory pathway was concealed. Intraoperative epicardial and endocardial mapping showed 10 left free wall pathways, seven septal pathways, and four right free wall pathways. One patient had two right free wall accessory pathways. There was one postoperative death (from a ruptured cerebral haemangioma) and one patient had transient hemiparesis. There was early recurrence of arrhythmia or pre-excitation in six patients and five of these were among the first ten in the series. Four of the six underwent successful reoperation; 17 patients remain symptom free of all antiarrhythmic treatment. Two patients did not undergo reoperation—one became symptom free on drugs that had previously been ineffective and the other received an antitachycardia pacemaker. The mean period of follow up was six years.

Accessory pathway function was not restored and atrioventricular nodal function was preserved in all patients, demonstrating the feasibility of this technique in the long term management of patients with the pre-excitation syndrome.

Since surgical operation in patients with Wolff-Parkinson-White syndrome was first attempted in 1967[1] and described definitively in 1968[2] various techniques of dissection or cryoablation have been used to ablate the accessory pathway.[3 4] Ablation by endocardial dissection must be performed under induced cardiac arrest in the open heart. Cryosurgery may obviate the need for extensive endocardial dissection[4] and may, combined with dissection, be applied to the epicardium without necessarily opening the heart.[5 6]

We have used cryosurgery as the primary mode of ablation of accessory atrioventricular pathways since 1977 and report our long term follow up as well as the immediate results.

Patients and methods

Between 1977 and 1985 238 patients undergoing electrophysiological study were shown to have accessory atrioventricular pathways. Of these, 186 were successfully treated medically, 13 had antitachycardia pacemakers implanted, and 19 required no treatment. Twenty patients (11 female, 9 male), aged 21—58 (mean 39) years had an operation (table). All had presented with paroxysmal orthodromic atrioventricular reentrant tachycardia. Six had also experienced paroxysmal atrial fibrillation with anterograde conduction across the accessory pathway and three of them had been resuscitated from ventricular fibrillation. In 16 pre-excitation was overt whereas in four it was concealed. Sustained orthodromic atrioventricular reentry tachycardia was inducible in all patients; one also had antidromic tachycardia. The indications for operation were failure of medical management in 13 patients with paroxysmal reentrant atrioventricular tachycardia, refusal of medical treatment in another, and atrial

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Table *Accessory pathway location and outcome in patients undergoing surgical cryoablation*

Patient	*Age at operation*	*Sex*	*Pathway location*	*Arrhythmia recurrence*	*Reoperation*	*Clinical outcome*	*Follow up (years)*
1	27	F	Right free wall (2)	−	−	1	10·2
2	46	M	Left posteroseptal	−	−	1	10·1
3	21	F	Right posteroseptal	+	+	1	9·5
4	36	M	Right posteroseptal	−	−	1	9·2
5	47	F	Left free wall	−	−	1	8·8
6	40	F	Left free wall	+	−	3	8·7
7	58	F	Left posteroseptal	+	−	2	8·6
8	48	F	Left free wall	+	+	1	8·5
9	49	F	Left free wall	−	−		*
10	40	F	Left free wall	+	+	1	6·2
11	49	M	Right posteroseptal	−	−	1	6·1
12	36	M	Left free wall	−	−	1	5·9
13	41	M	Left posteroseptal	−	−	1	4·6
14	41	M	Right free wall	−	−	1	3·9
15	30	M	Left free wall	−	−	1	2·8
16	33	F	Left freewall	+	+	1	2·7
17	42	M	Left free wall	−	−	1	2·3
18	21	F	Right posteroseptal	−	−	1	1·1
19	38	M	Right free wall	−	−	1	1·1
20	29	F	Left free wall	−	−	1	1·0

Clinical response 1, asymptomatic; 2, asymptomatic on previously ineffective medication, 3, no improvement
*Died suddenly 24 hours after operation from rupture of a cerebral haemangioma

fibrillation with rapid ventricular response in six. The 13 patients with atrioventricular tachycardia had received atrioventricular nodal blocking drugs as well as class I agents; the six patients with atrial fibrillation had also received class I agents and five had been given amiodarone, without success.

ELECTROPHYSIOLOGICAL STUDY

Electrophysiological study was carried out before and after surgery in all patients.[7] Intraoperative electrophysiological mapping was carried out with atrial and ventricular reference electrodes and a hand held exploring electrode.[8] Detailed and precise atrial and ventricular mapping was performed to determine the pathway location.[5] Electrophysiological study was repeated 6–10 days after operation.

SURGICAL TECHNIQUE

Cardiopulmonary bypass was started in the standard manner. All applications of the cryoprobe were made during continuous coronary perfusion without aortic cross clamping. Transient suppression of preexcitation during temporary cryothermia was used to confirm the pathway location[4] (figs 1 and 2). Cryoablation was first performed epicardially at the site of earliest atrial and/or ventricular activation in the atrioventricular groove[4] for a maximum of five minutes. If this epicardial approach was unsuccessful the accessory pathway was located by endocardial mapping and the cryoprobe was applied. Right sided pathways were approached by a right atriotomy and those on the left side by opening the atrial septum through a right atriotomy. During this procedure temporary ventricular fibrillation was induced to prevent air embolism; when the mitral valve was made regurgitant and an aortic vent incision made the heart was defibrillated and endocardial mapping and ablation performed. A similar procedure, in reverse order, was undertaken during closure of the heart.

In patients 1–8 single discrete cryolesions were used until accessory pathway conduction was abolished. From patient 9 onwards at least three contiguous lesions were made even if accessory pathway conduction was abolished by the first.

Septal cryolesions were delivered while atrioventricular conduction was monitored, and cooling was stopped immediately atrioventricular block occurred.

Results

ELECTROPHYSIOLOGICAL MAPPING

Intraoperative mapping confirmed the presence of an accessory atrioventricular connection in each patient and in one patient two right free wall pathways were found.

SURGICAL RESULTS

Two of the 10 left free wall pathways were ablated epicardially; one required additional dissection through the epicardial fat pad in the atrioventricular groove. In seven of the remaining eight, accessory pathway conduction was abolished by endocardial cryoablation. In the eighth, permanent interruption of the accessory pathway could not be achieved at the

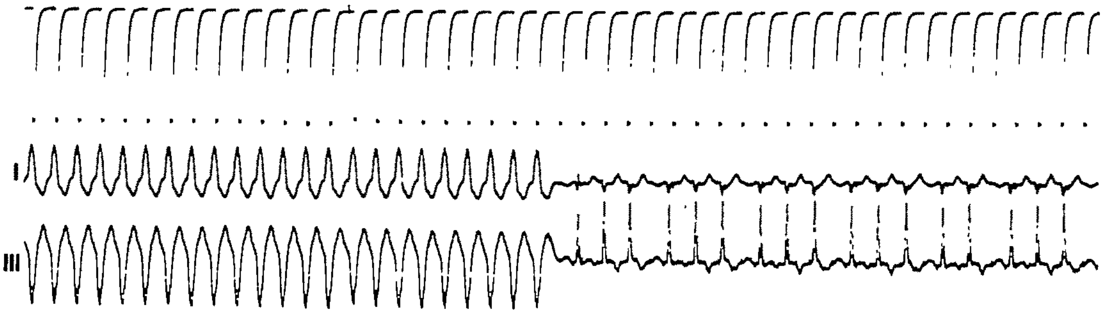

Fig 1 *During continuous atrial pacing (top) application of the cryoprobe to the site of the accessory pathway resulted in the disappearance of pre-excitation and conduction from atria to ventricles occurred across the atrioventricular node, with type 1 second degree block.*

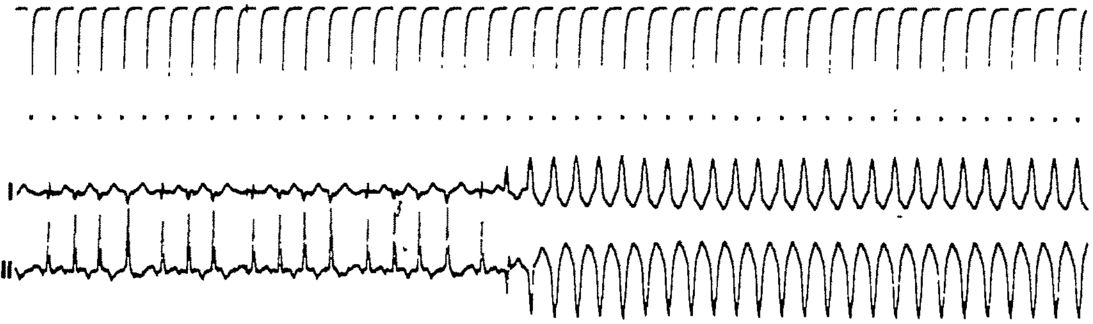

Fig 2 *Removal of the cryoprobe and rewarming of the site of pre-excitation was followed by restoration of 1:1 atrioventricular conduction across the accessory pathway.*

first operation despite both epicardial and endocardial freezing. At reoperation epicardial dissection and cryoablation did not succeed but repeat endocardial freezing was effective. Of the four right free wall pathways, one was successfully ablated by the epicardial approach and the remainder were ablated endocardially. All seven posteroseptal pathways required endocardial cryoablation. In those with right free wall and posteroseptal accessory pathways, pre-excitation was absent at the end of the operation.

POSTOPERATIVE ACCESSORY PATHWAY FUNCTION

In five patients accessory pathway conduction was present either at the end of the operation (two cases) or recurred within 24 hours. Of the five, arrhythmia recurred early in three and prompt reoperation was successful in all. In the fourth, accessory pathway behaviour was unchanged after the operation although spontaneous arrhythmia did not recur until three months later; reoperation then was successful. In the fifth, electrophysiological testing showed impaired anterograde accessory pathway conduction and reoperation was not performed. Reentrant tachycardia recurred after three months and has been controlled successfully with an implanted antitachycardia pacemaker.

POSTOPERATIVE COMPLICATIONS

One patient died 24 hours after operation. A ruptured cerebral haemangioma was found at necropsy. In another patient there was transient hemiparesis. In a third who had a septal accessory pathway there was transient complete atrioventricular nodal block which resolved within 10 days and has not recurred.

Long term follow up has ranged from 1 to 10 years (mean 6). Tachycardia recurred in a further patient after three months: postoperative electrophysiological study had shown normal anterograde conduction and apparent abolition of the concealed accessory atrioventricular pathway. This patient remains free of arrhythmias on medications that had previously been unsuccessful.

Discussion

In the Wolff-Parkinson-White syndrome, arrhythmia may be troublesome and is sometimes life threatening.[9] Not all patients respond to medications and their long term use, even when successful, may be associated with adverse effects. More specifically, in patients with this syndrome a short anterograde effective refractory period of the accessory pathway is associated with a rapid ventricular response to atrial fibrillation which may induce ventricular fibrillation.[10]

Surgical operation may offer definitive cure of the pre-excitation syndrome, abolish the incidence of atrial fibrillation,[11] and obviate the need for medication. The first definitive surgical interruption of an accessory pathway used atrioventricular disconnection.[2] This was superseded by the use of cryosurgery[4] which has undergone considerable modification.[5 6] Other techniques, notably endocardial dissection with or without cryoablation, are also successful[3 12] and surgical operation is now used extensively.[13 14] The well substantiated success rate of the endocardial approach will also determine the method chosen by individual institutions.[3]

Advantages of the cryosurgical technique include the production of a well demarcated area of damage[15] and the ability to interrupt conduction transiently before permanent ablation is performed (figs 1 and 2). Although an open heart procedure with cardiopulmonary bypass may sometimes be avoided[16] this will not be possible if other procedures, such as valve surgery, are required at the same time.

Septal accessory pathways may present difficulties because of the proximity of the specialised conduction system and, in the case of cryosurgery, the increased thickness of the atrioventricular tissue in this region. In this series, however, cryosurgery, in some cases from both sides of the septum, effectively ablated all seven septal pathways.

In a recent study which included a general review, delta waves recurred in approximately 12% of 388 patients, many of whom had required reoperation.[13] Antiarrhythmic treatment which had been unsuccessful before operation was often successful thereafter. In six of our patients pre-excitation recurred. In five this was early, within 24 hours of operation; in four reoperation was carried out and was successful. In the fifth patient the presence of excessive adipose tissue on the epicardial and endocardial aspects of the atrioventricular groove made accurate localisation uncertain and effective cryoablation impossible. Limited endocardial dissection was also unsuccessful and reoperation was not advised. The sixth patient had recurrence of arrhythmia after three months despite apparently successful pathway ablation as judged at electrophysiological reinvestigation 10 days after the operation.

This relatively high frequency of recurrence probably reflects early experience with this technique. Intraoperative mapping showed the pattern of pre-excitation and its participation in arrhythmia to be the same as that during the first operation, suggesting temporary damage to the accessory pathway rather than the presence of widely separated multiple bypass tracts.[17] After the recurrence of arrhythmia in patient 8, in whom a single cryolesion was used at the first operation, at least three adjacent cryolesions were used.

The length of follow up after surgery in these patients confirms the usefulness of this technique in the long term management of the pre-excitation syndrome. Most patients are well, require no treatment, and lead normal lives. Technical improvements have led to better immediate results in the later patients, but should pre-excitation recur early it can be controlled by reoperation with good expectation of the maintenance of normal atrioventricular conduction and abolition of the presenting arrhythmia.

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Plasma atrial natriuretic polypeptide concentrations during and after reversion of paroxysmal supraventricular tachycardias

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SUMMARY Plasma concentrations of immunoreactive atrial natriuretic polypeptide were raised in 22 of 23 patients with paroxysmal supraventricular tachycardia and in all seven patients with atrial flutter. Plasma concentrations of atrial natriuretic polypeptide rose soon after the onset of supraventricular tachycardia. A sample taken 30 minutes after reversion to sinus rhythm (pharmacological or non-pharmacological) showed a significant fall in 19 of the 23 patients with paroxysmal supraventricular tachycardia and all seven patients with atrial flutter.

Because atrial natriuretic polypeptide has powerful natriuretic and diuretic properties, an increase may contribute considerably to the polyuria that is often associated with episodes of supraventricular tachycardia.

Mammalian atrial tissue has been shown to contain secretory-like storage granules with characteristics similar to those of endocrine peptide secretory cells.[1 2] These granules were shown to contain a polypeptide hormone, which is first synthesised as a 151 amino acid prohormone.[3 4] The prohormone is further processed to several smaller peptides, one of which is α natriuretic polypeptide, a 28 amino acid polypeptide with potent natriuretic, diuretic, and vasorelaxant properties.[5–7]

The physiological role of atrial natriuretic polypeptide, or indeed any of the post-translational products, is unknown; however, there is a considerable body of evidence to suggest that this peptide may help to maintain sodium ion and water balance and modulate the renin-angiotensin aldosterone system.[8] A major stimulus for the release of atrial natriuretic polypeptide into blood seems to be atrial distension produced by volume loading or increased dietary intake of sodium ion.[9 10]

Paroxysmal supraventricular tachycardias are often associated with considerable polyuria and reports of raised concentrations of plasma atrial natriuretic polypeptide in such patients suggest that this substance may account for the combined diuresis and natriuresis.[11–13]

We measured plasma concentrations of atrial natriuretic polypeptide before and after reversion to sinus rhythm in patients with paroxysmal supraventricular tachycardia and those with atrial fibrillation or flutter.

Patients and methods

PATIENTS

This study was carried out within the guidelines set down by the National Health and Medical Research Council of Australia and was approved by the institute's human ethics advisory committee.

We studied twenty three patients admitted to our casualty department with paroxysmal supraventricular tachycardia (18 women and 5 men, aged 17–81 (mean 53) years). Diagnosis was confirmed by 12 lead electrocardiography which showed a regular, narrow QRS tachycardia in all 23 patients. Patients with acute or chronic congestive cardiac failure were specifically excluded.

In addition, we studied seven patients (five men and two women (mean age 60) with atrial fibrillation or flutter and five control patients (three men and two women (mean age 50)) without arrhythmias who had had intravenous lines inserted in the casualty department for other indications.

Renal function was assessed in all patients. Plasma

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creatinine concentrations were within the normal range (0·06–0·12 mmol/l) in all but two patients (0·14 and 0·21 mmol/l).

Fifteen patients were receiving concomitant medication when they were studied. This included a β blocker in one, β blocker plus digoxin in two, digoxin alone in one, quinidine in two, verapamil in one, diuretic agents in three, theophylline in one, thyroxine in two, and non-steroidal anti-inflammatory drugs in two.

A first blood sample was taken after insertion of a peripheral intravenous line and before attempted reversion and a second sample was taken 30 minutes after reversion to sinus rhythm.

BLOOD COLLECTION AND RADIOIMMUNOASSAY OF ATRIAL NATRIURETIC POLYPEPTIDE IN PLASMA

Blood collection and extraction

Venous blood (10 ml) was collected into a chilled tube containing edetic acid and aprotinin (10 000 units; Bayer, Australia). We took care to avoid haemolysis, which causes loss of immunoreactive atrial natriuretic polypeptide in plasma. Plasma was separated immediately by centrifugation, snap frozen, and stored at − 20°C until assay.

Extraction of plasma

Plasma (1 ml) was extracted overnight at 4°C with 1·8 ml acidified ethanol (95: 5 parts of 95% ethanol: 6 mol/l acetic acid) followed by centrifugation, and lyophilisation of the supernatant. The dried extract, equivalent to 1·0 ml of plasma, was reconstituted with 0·50 ml of assay buffer (radioimmunoassay section) and assayed for atrial natriuretic polypeptide.

The efficiency of the extraction procedure was determined for each patient's sample by the addition of radiolabelled human α atrial natriuretic polypeptide to a separate 1 ml volume of patient's plasma. This plasma was extracted as described above. After reconstitution in assay buffer (0·50 ml) a 200 μl volume was taken and its radioactive content measured and recovery was estimated. Recovery of radiolabelled human α atrial natriuretic polypeptide from plasma samples from both the controls and the patients was 78(6)% (mean (SEM)).

Radioimmunoassay of atrial natriuretic polypeptide

Assay buffer.—For all procedures in the assay we used 0·05 mol/l sodium phosphate buffered saline pH 7·4 containing aprotinin (250 U/ml), edetic acid (0·01 mol/l), 0·25 g % bovine serum albumin (Sigma Chemical, radioimmunoassay grade), and thiomerosal (0·6 mmol) (Sigma Chemical, as a preservative).

Specificity and characterisation of antiserum.—Antiserum to atrial natriuretic polypeptide 1–28 was raised in sheep after conjugation of synthetic human α atrial natriuretic polypeptide 1–28 to bovine thyroglobulin (Sigma Chemical USA) with ethylcarbodiimide (Pierce Chemicals, USA). The antiserum cross reacted to an equal degree with atriopeptins I, II, III, but it did not cross react with cardiodilatin 1–16, angiotensin II, vasopressin, oxytocin, neuropeptide Y, somatostatin, β endorphin, leu and met enkephalins and dynorphins 1–8 and 1–13.

We used the MK model extended least squares non-linear curve fitting program to analyse antibody binding affinity. Two binding sites were found: the first had a dissociation constant (Kd) of 37·58 pmol/l and affinity constant (Ka) of 2·7 × 10 l/pmol and the second a Kd of 122·5 pmol/l and Ka of 0·08 × 10 l/μmol.

Radioimmunoassay was carried out in 10 × 75 mm borosilicate glass tubes under non-equilibrium conditions at 4°C. Duplicate volumes (0·20 ml) of the plasma extract were incubated with 100 μl of sheep antiserum to human α atrial natriuretic polypeptide (final concentration 1:6000), followed by a further two day incubation, after the addition of 100 μl of (3-[^{125}I] iodotyrosyl 28) α atrial natriuretic polypeptide (5000 counts/min equivalent to 1–2 pg tracer mass) (Amersham, Australia). Synthetic human α atrial natriuretic polypeptide was used to generate a standard curve over the range 2–1000 pg/tube.

Bound and free atrial natriuretic polypeptide were separated by the addition of 100 μl of carrier sheep serum (diluted 1:250) and 100 μl of donkey antisheep immunoglobulin serum (diluted 1:5) followed by incubation at room temperature for three hours and centrifugation. The pellet was counted in a NEN 1600 gamma counter (Nuclear Enterprises). Standards were set up in triplicate in the presence of 0·20 ml of an extract of charcoal stripped plasma (hormone free) so as to reproduce the assay conditions used for the patient plasma samples. Concentration of plasma atrial natriuretic polypeptide was determined from the standard curve, plotted as the logit-log of the ratio of bound counts of unknown to bound counts of the zero standard versus concentration (pg/tube). The standard curve was linear over the range 10 to 600 pg/tube and the sensitivity of the assay was 2 pg/tube (2 from the mean ± SD of the zero standard). The intra and inter assay variability were 8 and 15% respectively.

Characterisation of plasma atrial natriuretic polypeptide measured by radioimmunoassay.—Plasma samples collected before and after reversion were pooled separately, extracted as above, and the dried extracts were analysed by high pressure liquid chromatography on a C18 reverse phase column and with an acetonitrile linear gradient elution profile. Analysis of the column eluant showed one major peak of immunoreactivity for both the plasma samples that coincided with the elution profile of the synthetic human α atrial natriuretic polypeptide (results not shown).

The plasma extracts were further characterised by serial dilution experiments. Pooled extracts of plasma obtained before and after reversion diluted in parallel with the synthetic human α atrial natriuretic polypeptide standard (results not shown).

Concentration of atrial natriuretic polypeptide in controls.—Atrial natriuretic polypeptide was measured in blood samples from 34 normotensive healthy volunteers (14 men, 20 women) with normal dietary intake of sodium and electrolyte status which were treated and extracted as described above. Subjects remained seated for 15 minutes before a blood sample was taken between 9 am and 10.30 am. The upper and lower limits of the normal range were 70 pg/ml and 4 pg/ml respectively and no sex dependent differences were found (men 36 (14) pg/ml, women 33 (16) pg/ml) (mean (SEM)).

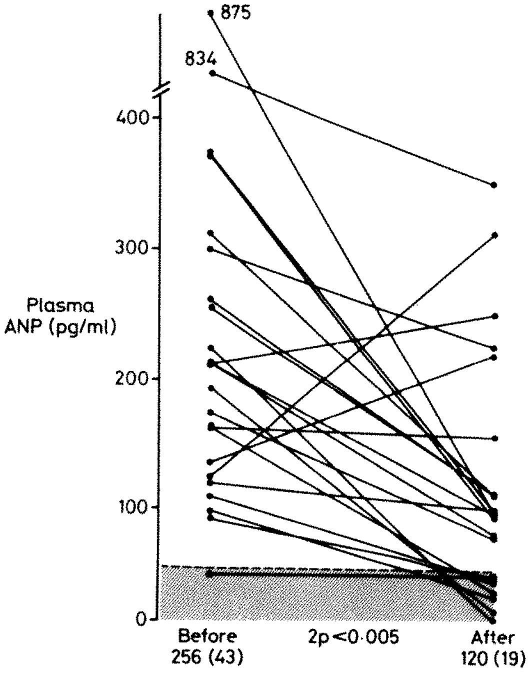

Fig 1 *Plasma concentration (mean(SEM)) of atrial natriuretic polypeptide (ANP) (pg/ml) before and 30 minutes after reversion in 23 patients with paroxysmal supraventricular tachycardia. The normal range is also shown.*

Results

Figure 1 shows plasma concentrations of atrial natriuretic polypeptide before and after reversion to sinus rhythm in the 23 patients with paroxysmal supraventricular tachycardia. During paroxysmal supraventricular tachycardia 22 of 23 patients had atrial natriuretic polypeptide concentrations above the upper limit for normal subjects in this laboratory (70 pg/ml). In one patient plasma atrial natriuretic polypeptide was within the normal range and did not change after reversion. Paroxysmal supraventricular tachycardia was converted to sinus rhythm by intravenous verapamil (1–20 mg) in 16 patients, intravenous digoxin (250–500 μg) in one, vagal manoeuvres in three, or a combination of these in three. In 19 patients concentrations of plasma atrial natriuretic polypeptide fell 30 minutes after reversion, in five to within the normal range. The mean concentration of plasma atrial natriuretic polypeptide was 256 (43) pg/ml before reversion and 120 (19) mg/ml 30 minutes after reversion ($2p < 0{\cdot}005$ by paired Student's *t* test). The fall in the concentration of atrial natriuretic polypeptide seemed to be independent of the mode of reversion of paroxysmal supraventricular tachycardia.

There was a weak inverse relation between the rate of paroxysmal supraventricular tachycardia (140–220 beats/min) and plasma concentrations of atrial natriuretic polypeptide ($r = -0{\cdot}45$, $p = 0{\cdot}017$ by

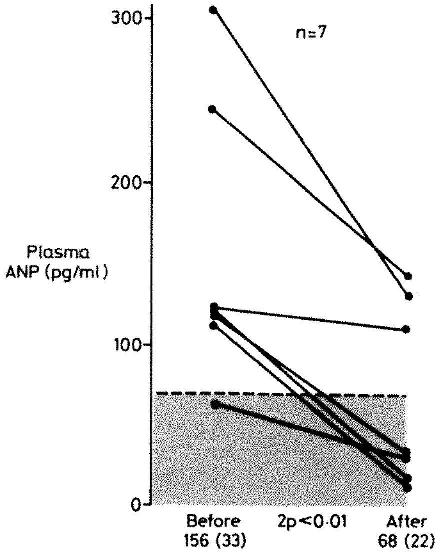

Fig 2 *Plasma concentration (mean(SEM)) of atrial natriuretic polypeptide (ANP) (pg/ml) before and 30 minutes after reversion in seven patients with atrial fibrillation or flutter. The normal range is also shown.*

Pearson's test). The duration of paroxysmal supraventricular tachycardia (10 min–3 days) had no apparent effect on plasma atrial natriuretic polypeptide concentrations; one patient had considerably raised plasma atrial natriuretic polypeptide (84 pg/ml) with paroxysmal supraventricular tachycardia lasting only 10 minutes.

In the seven patients with atrial fibrillation or flutter, plasma concentrations of atrial natriuretic polypeptide were raised before reversion was attempted (156 (33) pg/ml) and fell after reversion (68 (22) pg/ml) (fig 2).

Discussion

Our results show that patients with supraventricular tachycardia, particularly paroxysmal supraventricular tachycardia, and atrial fibrillation or flutter have considerably higher plasma concentrations of atrial natriuretic polypeptide than healthy controls. These results are consistent with earlier studies of small numbers of patients and animal studies.[13-19] Given that atrial natriuretic polypeptide has natriuretic and diuretic properties, the increase may account for the polyuria reported in patients with supraventricular tachycardias.[12 20 21] Others have suggested that the polyuria may be caused by suppressed vasopressin release[21 22]; however, such a mechanism does not account for the striking natriuresis associated with this condition.[20]

Plasma concentrations of atrial natriuretic polypeptide may rise early after the onset of paroxysmal supraventricular tachycardia and remain raised for prolonged periods of tachycardia, independent of clinical indices of left ventricular failure. The weak inverse relation between the rate of paroxysmal supraventricular tachycardia and plasma concentrations of atrial natriuretic polypeptide remains unexplained. One possible explanation is that the atrial cardiocyte becomes fatigued and supplies of atrial natriuretic polypeptide are exhausted. This would be an unusual phenomenon in endocrine cells but would be consistent with the fall in concentrations of atrial natriuretic polypeptide during tachycardia in one of the patients with atrial flutter (119 pg/ml to 44 pg/ml) that occurred without a change in rate of tachycardia and before reversion was attempted.

Although atrial pressure increases in this type of tachycardia and may act as the stimulus for secretion of atrial natriuretic polypeptide,[11] alternative intrinsic mechanism(s) associated with the arrhythmias could also mediate release of atrial natriuretic polypeptide. Further studies will be required to elucidate the mechanism(s) responsible.

In conclusion, supraventricular tachycardia (and paroxysmal supraventricular tachycardia in particular) are associated with raised concentrations of plasma atrial natriuretic polypeptide that fall rapidly and apparently independently of the mode of reversion whether this is pharmacological or non-pharmacological.

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Bedside nuclear probe for detection and quantification of left to right intracardiac shunts

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SUMMARY A cadmium telluride nuclear probe with an Elscint gamma camera was used to detect and measure left to right intracardiac shunts at the bedside in 34 patients. Fifteen also had right heart catheterisation and oximetric measurement of the shunt. For the nuclear technique 740 MBq (20 mCi) of technetium-99m pertechnetate was injected into the right antecubital vein and the pulmonary to systemic flow ratio (QP:QS) was measured by the gamma variate technique. Data were not obtained in four patients because the nuclear probe failed in three patients and one storage disc was corrupted. Data from the gamma camera were lost in another patient. When the size of the shunt measured by the nuclear probe was compared with that measured by the oximetric technique the mean difference (SD of mean difference) was 0·36 (SD 0·78) and when it was compared with the gamma camera it was 0·08 (SD 0·67). Analysis of scatter plots showed that the larger the shunt, the larger the discrepancy. Twenty four of 29 data sets showed complete agreement between the nuclear probe and gamma camera on the size of the shunt. Any differences were small.

These data indicate that left to right intracardiac shunts may be measured accurately by a nuclear probe at the bedside in either the coronary care unit or outpatient department.

A method for detecting and measuring left to right intracardiac shunts at the bedside would be useful. It could rapidly confirm the clinical diagnosis of suspected rupture of the interventricular septum in outpatients and in the coronary care unit.

Earlier studies have shown good agreement between the results of a radionuclide technique and oximetry[1-3] and some believe that the radionuclide technique is more accurate.[4] We have compared the estimates of intracardiac shunts measured by a gamma camera and by a miniaturised cadmium telluride nuclear probe with those of standard oximetry.

Patients and methods

To test the discriminatory function of the radionuclide technique we studied 28 patients (mean (range) age 38 (14–72)) with suspected left to right shunts and a further six with either impaired left ventricular function or mitral regurgitation. Fifteen patients in whom clinically significant shunts were suspected also had right heart catheterisation and oximetric measurement of the shunt.

Two experienced consultant radiologists independently reported on the size of the shunts from standard chest *x* rays and graded the size of the shunt (A = no shunt; B = QP:QS <2:1; and C = QP:QS >2:1).

RADIONUCLIDE TECHNIQUE

A first pass radionuclide angiogram was acquired in the anterior projection simultaneously for both the gamma camera and nuclear probe. Data were collected in list mode by an Elscint gamma camera linked to a PDP 11 computer. Two miniaturised cadmium telluride detectors were positioned on the anterior chest wall and the patient was positioned under the gamma camera. One nuclear probe was located over the clavicular region to indicate the compactness of the bolus at the superior vena cava and the other was positioned over the right lung to detect a left to right shunt, which is shown by a prolongation of the normal time activity curve. During the study we

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found it necessary to provide additional collimation for these probes to prevent pick up of activity in adjacent areas (for example the superior vena cava and aorta).

These probes were connected to a solid state memory recorder (Memolog −500, Novo Diagnostics). The data were later transferred to the PDP 11 computer, which was used to calculate the size of the shunt. The patient's red cells were prepared for in vivo labelling by a preliminary intravenous injection of (inactive) pyrophosphate and stannous ion. Twenty minutes later, 740 MBq (20 mCi) of technetium-99m pertechnetate was injected into the right antecubital vein. The nuclear probe would require 150 MBq (4 mCi) of technetium-99m when used alone.

Early in the study the bolus was injected through a 18G Venflon. Because some of the injections gave a fractionated bolus the injection technique was modified. The Venflon was connected to a short length of clear tubing which was connected to a three-way tap. A 1 ml syringe containing 99m Tc was connected to the side arm and a 50 ml syringe of saline was connected to the other. The three-way tap and tubing were loaded with saline. The dose of technetium, marked on both sides by a small air bubble, was advanced into the clear tubing and on into the Venflon by means of the saline syringe. This bolus was then injected rapidly into the antecubital vein. This method gave a good non-fractionated bolus in most patients.

The time-activity curves from both systems were analysed by the same method. A time-activity curve from the superior venacaval region of interest was used to check that the bolus was not fractionated. The gamma camera was used to image the superior vena cava and a region of interest over the right lung was entered visually, whereas with the nuclear probes this information was taken directly from the detectors. If the time-activity curve from a region of interest over the right lung was acceptable it was analysed by gamma variate fits.[2 3] Where the bolus was attenuated we used deconvolution analysis[5-7] to correct the lung time-activity curve before the shunt was calculated.

We used the same software (Gamma 11) for gamma variate fitting for data from both the gamma camera and the nuclear probe, which were both written to a file on disc in the same format.

OXIMETRIC TECHNIQUE

During right heart catheterisation paired blood samples were taken from the inferior vena cava, low, mid, and high right atrium, superior vena cava, apex, mid, portion, and outflow of the right ventricle, and main pulmonary artery. An arterial sample was obtained from a femoral needle puncture. The samples were taken in rapid sequence once the patient was considered to be physiologically stable. The oxygen saturation was measured with a reflectance oximeter.[8 9] The pulmonary to systemic flow was calculated by the formula:

$$\frac{QP}{QS} = \frac{\text{systemic arterial } So_2 - \text{mixed venous } So_2}{\text{pulmonary venous } So_2 - \text{pulmonary arterial } So_2}$$

where So_2 is the oxygen saturation. The mixed venous oxygen saturation was estimated from saturation in the superior vena cava (SVC) and inferior vena cava (IVC) by the formula[10]:

$$\text{Mixed venous } So_2 = \frac{3 \times \text{SVC } So_2 + \text{IVC } So_2}{4}$$

DATA ANALYSIS

The calculated pulmonary to systemic flow ratios calculated by both techniques were compared by constructing scatter plots and calculating the standard deviation about the mean difference. Correlation coefficients were not calculated because according to Altman and Bland they are not appropriate in method comparison studies.[11] Only the lines of identity are shown in the figures. The important question is how well the two measures agree? We calculated the difference between the two measurements for each subject. The mean of these differences is a measure of the accuracy (bias) and the standard deviation is a measure of precision. The size of the shunt was graded arbitrarily: 1 = no shunt; 2 = QP:QS from 1·3:1 to 1·5:1; 3 = QP:QS from 1·6:1 to 2:1; and 4 = >2:1.

To compare shunt size as graded by the radiologists and by the nuclear techniques the arbitrary grading was transformed to that used by the radiologists. This change was used solely to compare the shunt sizes as graded by the radiologists with the sizes given by nuclear techniques.

Results

Thirty four patients were recruited into the study. Four data sets were rejected—three because of failure of the nuclear probe and another patient's data were lost when the storage disc was corrupted and one patient's data lost from the gamma camera because of technical problems. This left 29 data sets for comparison of the nuclear probe and gamma camera and 30 data sets for the comparison of the nuclear probe and radiologists.

The size of the shunt as estimated by the nuclear probe and gamma camera showed complete accord in 24 patients and discord in five patients (table 1). When the nuclear probe was compared with

Table 1 *Concordance of size of shunt*

	Complete agreement	*Disagreement (by 1 grade)*	*Disagreement (by 2 grades)*
Gamma camera *vs* nuclear probe	24	5	—
Nuclear probe *vs* oximetry	11	4	—
Gamma camera *vs* oximetry	8	6	—
Nuclear probe *vs* first radiologist	11	16	—
Nuclear probe *vs* second radiologist	14	13	3
Radiologist 1 *vs* radiologist 2	17	9	4

One set of data from the gamma camera was lost. This set came from one of the patients who underwent right heart catheterisation with oximetry.

oximetry there was complete concordance in 11 patients and minor variation in four patients (table 1). For the comparison of the gamma camera and oximetry the figures were eight and six respectively. There was some discordence between each radiologist but there was greater discordence between each radiologist and the nuclear probe (table 1).

The individual values for agreement for various comparisons are shown in the scatter plots and frequency histograms (figs 1–3). Table 2 shows the mean of differences between the methods and their respective standard deviations.

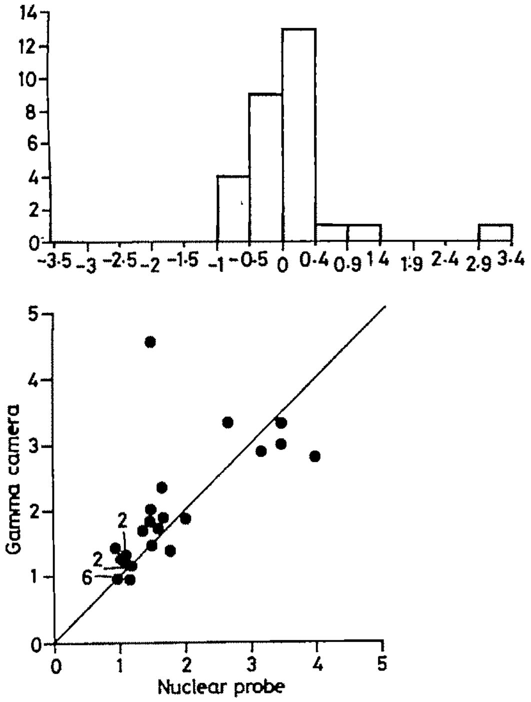

Fig 1 *Scatter plot and frequency histogram of the nuclear probe and gamma camera. (The line drawn is the line of identity.) The histogram represents the differences in shunt size between the two methods. The figures on the x and y axes indicate the shunt size. Where data points overlap by one or more points on the scatter plot the numbers of points are given.*

Generally there was a good agreement between the nuclear probe and standard gamma camera and between each isotopic method and oximetry. The larger the size of the shunt the greater the scatter of the data. This does not, however, affect clinical interpretation of the size of the shunt.

Discussion

The results reported in this study confirm the close agreement in the size of left to right shunts measured by the standard gamma camera and by the oximetric method. They also demonstrate that the cadmium telluride miniaturised nuclear probe provides estimates of shunt size that agree with the gamma camera and with the oximetric methods. During the

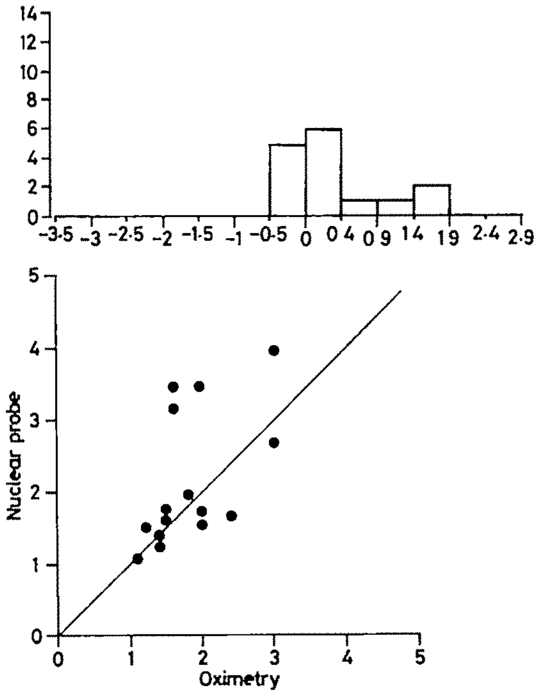

Fig 2 *Scatter plot and frequency histogram of oximetry and the nuclear probe. (Details of layout as for fig 1.)*

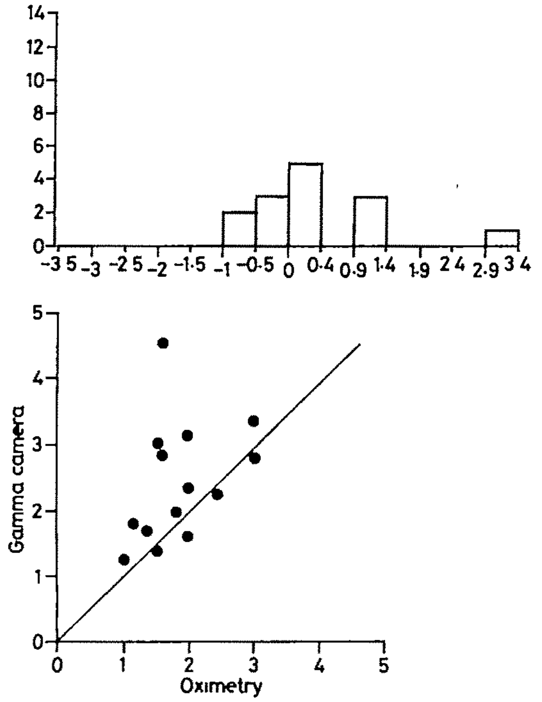

Fig 3 *Scatter plot and frequency histogram of oximetry and the gamma camera (Details of layout as for fig 1.)*

study there were a few minor changes to the technique. The injection of the bolus was improved as was collimation of the cadmium telluride crystal. These changes assisted processing by producing better curves but did not affect the final results. The size of the differences between the nuclear data and oximetric data was similar at the beginning and end of the study as were the differences between the nuclear probe and gamma camera. The nuclear probe, when used alone, needs only a quarter of the dose of radiopharmaceutical required for the gamma camera.

It was instructive to note the variation in shunt size as estimated by two experienced radiologists. We conclude that radiology is therefore at best a very rough guide to the clinical significance of the shunt size.

Table 2 *Mean (SD) shunt size for between-method comparisons*

	Mean difference	*SD of difference*
Nuclear probe *vs* gamma camera (n = 29)	0·08	0·67
Nuclear probe *vs* oximetry (n = 15)	0·36	0·78
Gamma camera *vs* oximetry (n = 14)	0·53	0·95

The cadmium telluride miniature probe can be used to detect left to right shunts and to estimate the size of the shunt. In most patients the results of the nuclear probe and gamma camera methods agreed on the size of the shunt (large, moderate, or small). The nuclear probe can therefore be regarded as a useful clinical tool. The nuclear technique becomes less accurate in three situations. It cannot be used to measure right to left shunts because it works on the principle of measuring the increased pulmonary transit time which does not occur in this situation. The time-activity curves, from which the shunt is calculated, may also be prolonged in severe left ventricular dysfunction and in pronounced mitral valve regurgitation, making estimation of the shunt size unreliable; however, we found no evidence of this effect in our data.

In many units the demand for the gamma camera is high. The cadmium telluride miniature detectors can provide useful data at a much lower cost than the gamma camera, and although no pictures are available the miniature detectors are easily portable and may be interfaced with a small microcomputer. This technique can be used in both the coronary care unit and the outpatient department. The nuclear technique complements cross sectional echocardiography, which will determine the site of the shunt. Ginzton *et al* showed that the combination of contrast cross sectional echocardiography and radionuclide shunt detection led to a proper diagnostic and therapeutic decision in 24 of 25 patients.[12]

We consider that the nuclear probe is a useful investigative tool in the determination of the pulmonary systemic flow ratio in patients with left to right intracardiac shunts.

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Intermediate to late term results of Mustard's procedure for complete transposition of the great arteries with an intact ventricular septum

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SUMMARY Overall survival after Mustard's operation was assessed in 130 patients with complete transposition of the great arteries and an intact ventricular septum who were operated on at the Brompton Hospital in the 12 year period from January 1974 to December 1985. Actuarial analysis showed a survival at five years of 79·1% (25 deaths in 130 patients). Half the deaths occurred within a month of operation and half up to five years later. Operation under the age of three months carried a greater mortality (six deaths in 11 patients). Statistical analysis showed that these survival figures were consistent throughout the series and did not alter with the year of operation.

In the light of recent trends in treatment of this lesion, it is concluded that for neonates an arterial switch procedure is now likely to carry the best chance of long term success. For the patient who presents after the age of three months, however, there may still be a place for the Mustard procedure.

Debate continues about the optimal surgical treatment for complete transposition of the great arteries with an intact ventricular septum. In many centres atrial redirection procedures (Senning or Mustard operation) have an acceptably low mortality.[1-3] The complications of these operations can be minimised by careful attention to operative detail.[4 5] In contrast, the operative mortality of the more recently introduced arterial switch procedure (which produces a more anatomically correct repair) was higher in the early reported series. It has now, however, been demonstrated that the overall results of the arterial approach can match or even surpass those of atrial redirection.[6]

When assessing the merits of these two procedures we must consider both their short term and long term outcome. Such analysis is possible for the atrial redirection procedure, but long term analysis is not as yet possible for the arterial switch procedure. To provide information on atrial redirection we have studied the immediate to late results of the Mustard operation by examining the records of 130 patients with complete transposition of the great arteries and an intact ventricular septum who were operated on by one surgeon at the Brompton Hospital over a 12 year period.

Patients and methods

Between January 1974 and December 1985, 136 patients born in Great Britain and attending the Brompton Hospital had a Mustard operation for complete transposition of the great arteries (concordant atrioventricular and discordant ventriculoarterial connections) with intact (or virtually intact) ventricular septation (any ventricular septal defect present was considered to be too small to warrant closure). All the patients with this abnormality who were referred to our hospital during this period were routinely followed up as outpatients at the Brompton Hospital, at Our Lady Hospital for Sick Children, Dublin, or at their referring hospital. Letters indicating the progress and health of the patient were sent to the consultants at the Brompton Hospital if the child was not followed up there. The notes of 130 of these patients were examined retrospectively. Six sets of

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notes could not be traced because of loss. Follow up in the studied patients was complete.

We recorded the age and sex of the patient, the year of operation, the source of referral (United Kingdom or Ireland), the cardiopulmonary bypass technique, whether or not profound hypothermia was used with circulatory arrest, the type of atrial baffle, the presence of either preoperative or postoperative rhythm problems or both, the presence of associated abnormalities, and the need for reoperation.

The quality of life was not assessed because this was considered inappropriate in a retrospective study. We are currently assessing this aspect by prospective objective (including formal exercise testing) and subjective tests.

Ninety patients were referred from hospitals in the United Kingdom and 40 from centres in Ireland. The age range was 3 days to 9 years 8 months with a mean age of 1 year 5 months. There were 97 boys and 33 girls. Circulatory arrest was used in 48 children during their operation while 82 had cardiopulmonary bypass. The baffle was made of dura mater in 24 cases, of Dacron in 68 cases, of bovine pericardium in 23, and of Teflon in one. In 14 cases, the type of baffle material used was not recorded in the notes.

Twenty four children had persistent patency of the arterial duct, 17 had left ventricular outflow trace obstruction of various types, nine had haemodynamically insignificant defects of the ventricular septum (which were not closed at surgery), two had aortic coarctation, and one patient had stenosis of the pulmonary valve.

The data were analysed and survival curves were plotted by actuarial methods.[7] The survival curves were compared and prognostic factors were examined by the log rank test[8] and Cox[9] models.

Results

Table 1 shows the age of operation and cumulative mortality for the 130 patients on whom follow up data were available. Twenty five (19%) of the 130 patients died. The death rate was significantly higher in children aged less than three months at the time of operation (fig 1 and 2). Analysis of the other variables and possible risk factors listed in the methods section showed that no other feature was significantly associated with length of survival. Trends were demonstrated with some variables but for the numbers of patients analysed none of the observed trends was statistically significant.

Six of the 24 children with a patent arterial duct died. Three of the 17 children with obstruction of the left ventricular outflow tract also died, although the gradients in these three were not significantly greater than the values for this overall subset. All those with an associated but haemodynamically insignificant ventricular septal defect, coarctation, or pulmonary valve stenosis survived operation. Thirteen patients had a second operation because of obstruction of the superior caval vein in five, pulmonary venous obstruction in four, inferior caval venous obstruction in three, and dehiscence of the patch around the suture line in the other. Four of these children died; three had been operated on because of presumed pulmonary venous obstruction. Two of these children were shown not to have pulmonary venous obstruction. In both the high pulmonary arterial pressure measured preoperatively reflected pulmonary vascular disease rather than obstruction. The distinction between the two conditions at catheterisation rests on the pulmonary arterial wedge pressure. This should be low in the setting of pulmonary vascular disease whereas, with venous obstruction, the pressure is high. Unfortunately, it is difficult to obtain true wedge (that is, pulmonary venous atrial) pressures in patients with pulmonary vascular disease. Because of this, a recorded high wedge pressure may not distinguish between pulmonary vascular disease and obstruction. The fourth death occurred in the perioperative period in a child who had thrombosis of the superior vena cava (see table 2).

Table 3 shows the time after the first operation until death. Half the group died within a month of operation and half more than one month after operation—deaths occurred up to five years after

Table 1 *Mortality related to age at operation**

Age at operation	*No of patients*	*Deaths*		*Overall (%)*
		Early	*Late*	
0–3 months	11	5	1	55
3 months–1 year	43	1	6	16
1–2 years	51	6	3	18
2–5 years	22	1	2	14
5–10 years	3	0	0	0
Total	130	13	12	19

*Later in the series younger patients will have shorter periods of follow up.
"Early" death refers to those within 30 days of operation

Table 2 *Reasons for reoperation and results of reoperation*

Indication for reoperation	*No of patients*	*Deaths*	*Cause of death*
SCV obstruction	5	1	Thrombosis in SCV
Pulmonary venous obstruction	4	3	Pulmonary vascular disease in two
ICV obstruction	3	–	
Patch dehiscence	1	–	
Total	13	4	

SCV, superior caval vein (vena cava), ICV, inferior caval vein (vena cava).

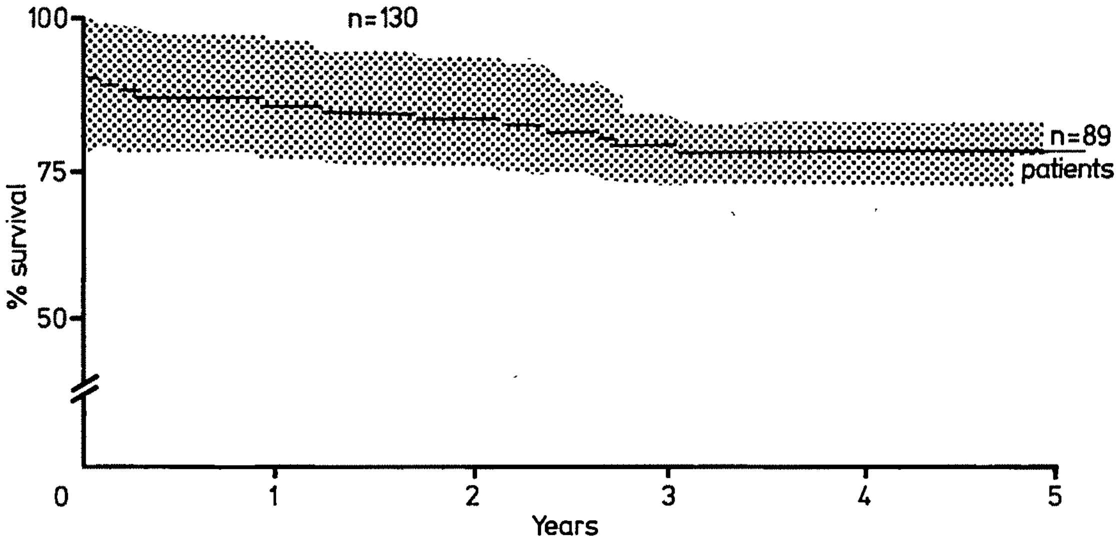

Fig 1 *Actuarial survival curve for the overall population. The stippled area shows the 70% confidence interval.*

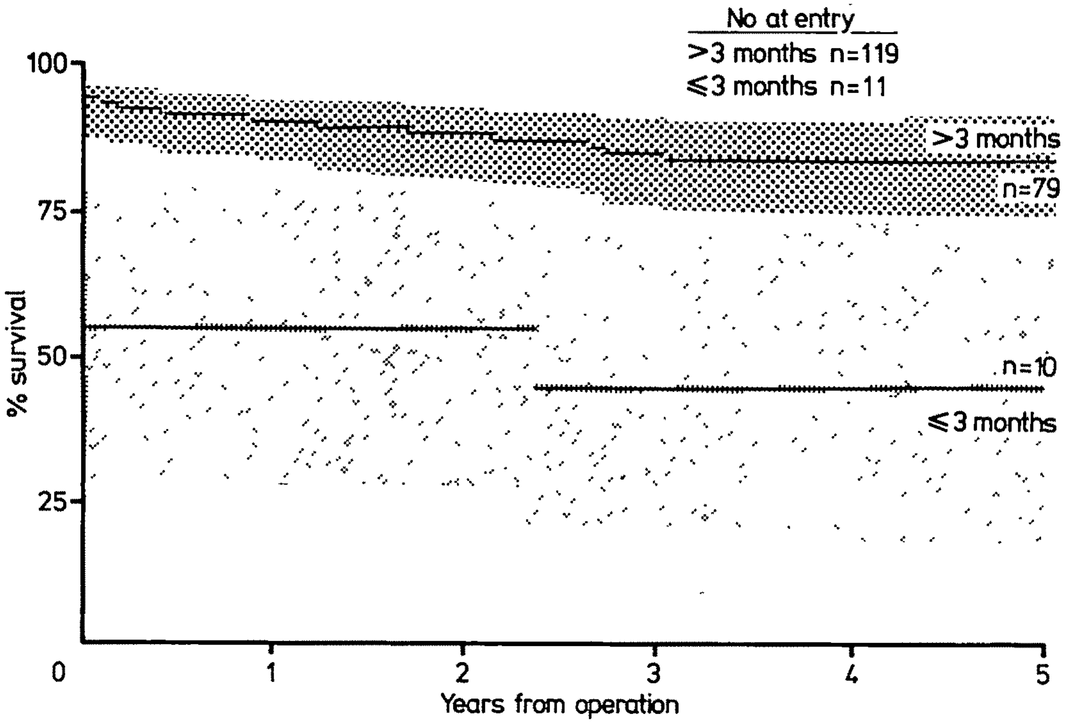

Fig 2 *Actuarial survival curves for the groups of patients aged over three months (n=119) or less than three months (n=11) at repair. The shaded areas show the 70% confidence intervals.*

Table 3 *Time until death after first operation*

Age at operation	*48 h*	*2 days–1 mnth*	*1 mnth–1 yr*	*1–2 yr*	*> 2 yr*	*Total*
3 mnth	4	1	–	–	1*	6
3 mnth–12 mnth	1	–	2	2*	2	7
12 mnth–24 mnth	2	4*	1	–	2	9
2–5 yr	1	–	1	–	1	3
Total	8	5	4	2	6	25

*Death caused by pulmonary vascular disease (one child in each case).

operation. Table 4 shows the causes of death (where they could be determined). Of the 11 children dying with low cardiac output, seven were known to have had postoperative arrhythmias. Four children had nodal rhythm (one of these was also in renal failure), two had periods of supraventricular tachycardia, and one was known to have atrial fibrillation. The other four children were in sinus rhythm. As stated previously all three children with pulmonary vascular disease died within two and a half years of operation; in one patient who died the Mustard procedure had been carried out as early as 11 weeks of age.

Necropsies on two children showed pulmonary venous obstruction (one five months and the other three years after operation). Neither of these children had had a second operation and, hence, are not included in table 3. Another child died of cerebral damage within two months of operation. Two children died suddenly. Death occurred 10 months after operation in the first and necropsy showed venous obstruction of the inferior vena cava. The other child had been treated for arrhythmias that developed nearly three years after operation. Electrocardiograms showed atrial flutter with 3:1 atrioventricular conduction. Direct current cardioversion and antiarrhythmic agents were used to control the arrhythmias but the child died suddenly two months after their onset.

Five children died after operation from causes not directly attributable to their cardiovascular state. Three died of respiratory infections between two and five years after operation. No other cause of death was known. One child died of gastroenteritis three months after operation and another died in the perioperative period after an oesophageal operation two years after the Mustard operation.

Table 4 *Cause of death*

Known cause of death	*No*	*Time after operation*
Low cardiac output/ cardiac arrest	11	10 within 7 days, 1 at 1 mnth
Pulmonary vascular disease	3	18–30 mnth
Respiratory infections	3	2–5 yr
Pulmonary venous obstruction	2	5 mnth and 3 yr
Cerebral damage after operation	1	2 mnth
Thrombosis in superior caval vein (vena cava)	1	1 week
Sudden death, obstruction of inferior caval vein (vena cava)	1	10 mnth
Sudden death, arrhythmias	1	2 yr 8 mnth
Gastroenteritis	1	3 mnth
In postoperative period after an oesophageal operation	1	
Total	25	

Discussion

There are protagonists for both the atrial[1 2] and the arterial[6 10] approaches for management of children with complete transposition of the great arteries with an intact ventricular septum. The best results published for each operation lend strong support to both viewpoints. As always, hospital rather than population based series raise the question of case selection. Do the surgical results of the given hospital forecast that were all the patients in the population with a particular anomaly to be operated on at that hospital similar results would be obtained? The surgical results in any centre will be improved if the sickest patients do not survive to reach hospital. For this reason, results for patients treated in one hospital may not be directly comparable with those in another. With these caveats in mind, each unit must try to determine the optimal treatment for complete transposition and intact ventricular septum on the basis of its own results, while taking note of results at other centres. In this study we have attempted to look critically at our own results for interatrial repair of complete transposition.

The overall five year actuarial survival was 79% (70% confidence interval 68% to 87%). Further analysis indicated that those who were less than three months old when they were operated on had a significantly worse five year actuarial survival (45% (70% confidence interval 21% to 72%)) than those operated on when they were older (82% (70% confidence interval 70% to 90%)). In all those who were less than three months at operation, operation was not undertaken electively. The indications were either failure to thrive or else persistently severe cyanosis with or without metabolic acidosis. It may well be that had atrial redirection been performed electively at an earlier age these results could have been improved. Against this must be set the results of other series[3 11] which have shown young age to be a risk factor for atrial redirection, albeit with the age cut off at one month rather than three months as in our series.

Can we now use this data to plan a protocol for the future management of patients referred to our centre with complete transposition and intact ventricular septum? For neonates it is difficult on the basis of our experience to counter the excellent results obtained in selected centres for the arterial switch procedures.[6] Bearing in mind the caveats discussed above, and also the lack of long term follow up for the arterial procedure (which cannot be overemphasised), it still seems that the arterial switch procedure will offer a better chance of long term survival for the neonate than the Mustard operation. This view is reinforced by finding that in our own centre 23 (18%) patients who had balloon atrial septostomy died before correction of the defect could be attempted.[12]

Nevertheless, our experience is limited to the Mustard variant of complete transposition. It could well be argued that the Senning operation, which is said to overcome the problems of venous obstruction and, possibly, rhythm disturbances, could improve the long term outcome of the redirection procedure. So far follow up after the Senning operation is also limited and as yet we see no compelling evidence to persuade us to change from one to the other atrial redirection procedure. We believe that for the neonate with complete transposition and intact ventricular septum the arterial switch procedure carries the better chance of success in our centre. Our own initial results with this approach[13] bear out this viewpoint, as do those from some other centres.[6 14]

But what of the patient referred after the neonatal period? Such patients continue to reach our wards. Here the solution is not nearly so clear cut. Preparative surgery would be required in such patients to make the arterial procedure a realistic alternative. The risks of these palliative procedures have not been analysed in the same depth as those for the arterial switch performed during the neonatal period. In this latter group, therefore, particularly those above the age of three months, we recommend the Mustard procedure. More rigorous analysis of the two stage arterial switch procedures may lead us to revise our opinion.

It was noteworthy that one child in our study developed pulmonary vascular disease and died despite having an operation at 11 weeks of age. It is known that high pulmonary vascular resistance (above 8 units/m^2) greatly increases the risk of Mustard's operation with intact ventricular septum. We have not, however, found other published reports of pulmonary vascular diseases progressing in children with simple complete transposition who had the Mustard operation before they were three months old.[15] The occurrence of such changes in even one patient in our series strongly supports the trend for earlier correction promoted by the use of the arterial switch procedure during the neonatal period.

We thank Professor Connor Ward of Dublin, who referred many patients for operation and made available their follow up data, and Dr Janet Darbyshire of the Medical Research Council external staff who gave valuable advice during the design of the study.

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Doubly committed subarterial ventricular septal defect: new morphological criteria with echocardiographic and angiocardiographic correlation

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SUMMARY To gain a better understanding of the anatomy of doubly committed subarterial defects and its relation to findings at cross sectional echocardiography and angiocardiography, eight necropsy specimens from patients with this condition were examined, and preoperative echocardiograms and angiocardiograms from 313 patients with surgically or necropsy confirmed outlet defect were reviewed. Of these, 48 had doubly committed subarterial defects. Morphological review showed that doubly committed defects are roofed by the arterial valves in fibrous continuity because of lack of both the outlet septum and the "septal" aspect of the subpulmonary infundibulum. Angiocardiography had a lower sensitivity (50%) than echocardiography (95%) for diagnosis of doubly committed defects, but each was highly specific. In five (14%) of 35 available echocardiograms the arterial valves were normally offset, but in the remainder they were at the same level. The ventriculoarterial connection was concordant in 37/48 (77%), discordant in five (10%) of 48, and double outlet right ventricle in six (13%) of 48. Displacement of the fibrous raphe between the arterial valves in relation to the ventricular septum below was associated with outflow obstruction in 14 patients (pulmonary in nine and aortic in five). These features were readily identified by echocardiography.

Thus echocardiography is not only a more accurate method than angiocardiography of recognising these defects, but also shows that the arterial pole of the heart is architecturally abnormal.

The doubly committed subarterial defect accounts for 5% of isolated ventricular septal defects in white populations[1] and 30% of such defects in oriental populations.[2] The course may be complicated by prolapse of the aortic leaflets, with or without regurgitation, pulmonary hypertension, aneurysm of the sinus of Valsalva, acquired aortic to ventricular communications, endocarditis, and the need for aortic valve replacement.[3] Prompt surgical intervention is recommended for aortic leaflet prolapse, with or without regurgitation, or if the defect is large.[4] This emphasises the need for swift and accurate diagnosis.

We reviewed the morphology of these defects to establish the criteria for diagnosis. We then compared the results of echocardiography and angiography in an effort to establish the strengths and weaknesses of the two techniques.

Patients and methods

We reviewed surgical and pathology records from July 1979–December 1986. Three hundred and thirteen patients had septal defects between the

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ventricular outlets confirmed at operation or necropsy. There were two groups. The first contained those with perimembranous or infundibular muscular defects. The second group comprised 48 patients with doubly committed subarterial defects.

Eight necropsy specimens were available from the 10 patients with doubly committed defects who died. The findings from these hearts were correlated with the results of echocardiography and angiocardiography.

Preoperative echocardiographic and angiocardiographic diagnoses of all 313 patients were noted. We reviewed 35 echocardiograms and 40 angiocardiograms that were available from patients with doubly committed defects. We looked for fibrous continuity between the leaflets of the aortic and pulmonary valves, offsetting of these valves, unequal division of the outflow tracts with overriding of one or other arterial valve, and prolapse of the aortic leaflets with or without aortic insufficiency.

Results

MORPHOLOGICAL REVIEW

The normal outlet (or infundibular) septum is the muscle separating the outflow tracts of the left and right ventricles. This extends cephaled to the tricuspid valve and ends opposite the attachment within the left ventricle of the right coronary leaflet of the aortic valve. It is usually a small structure. The remaining right ventricular outflow tract is a sleeve of muscle supporting the leaflets of the pulmonary valve. Piercing this muscle produces a passage leading outside the heart. The presence of this extensive subpulmonary infundibulum creates normal offsetting of the arterial valves, which is readily visualised by cross sectional echocardiography (fig 1).

In contrast, all eight hearts with doubly committed subarterial defects showed complete lack both of the outlet (infundibular) septum along with the "septal" aspect of the sleeve of subpulmonary infundibulum. In consequence, the interventricular communication was roofed by fibrous continuity between the leaflets of the aortic and pulmonary valves (fig 2). In one case there was considerable offsetting of the leaflets. The structure producing the offsetting was the wall of one aortic sinus rather than the muscular subpulmonary infundibulum, as in the normal hearts (fig 3). In some cases, there were remnants of infundibular muscle near the level of continuity between the valves that did not form a continuous muscle rim to roof the defect. Major associated anomalies in these eight hearts included double outlet right ventricle (one case), complete transposition (two cases), overriding aortic and dysplastic pulmonary valve (one case), and interruption or coarctation of the aortic arch (three cases).

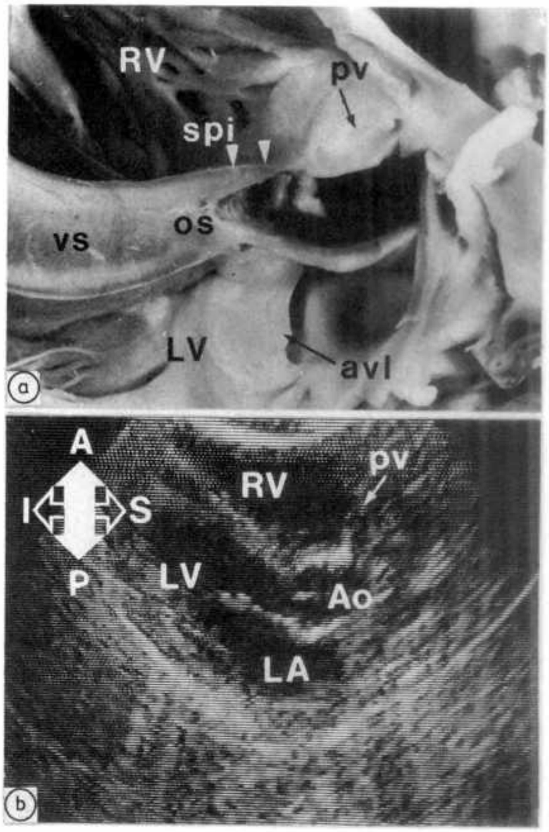

Fig 1 *(a) Photograph of a normal heart that represents a long axis echocardiographic view through the arterial valves and shows the relation of the left and right ventricular outflow tracts. The pulmonary valve is more cephalad than the aortic valve because of the extensive subpulmonary infundibulum. Only a relatively small area can be considered as outlet septum (the muscle separating the subpulmonary and subaortic outflow tracts). (b) Parasternal long axis echocardiogram of a normal heart showing the anatomy in (a). A, anterior; Ao, aorta; avl, aortic valve leaflet; I, inferior; LA, left atrium; LV, left ventricle; os, outlet septum; P, posterior; pv, pulmonary valve; S, superior; vs, ventricular septum; spi, subpulmonary infundibulum.*

In the unrepaired hearts, obstruction of ventricular outflow was associated with displacement (relative to the outflow tracts) of the fibrous raphe between the aortic and pulmonary valves with overriding of the unobstructed arterial valve, or alternatively, with thickening or dysplasia of the arterial valve leaflets themselves or both. One case showed additional redundant valve tissue adherent to the pulmonary valve producing "subvalvar pulmonary stenosis". In those with a displaced

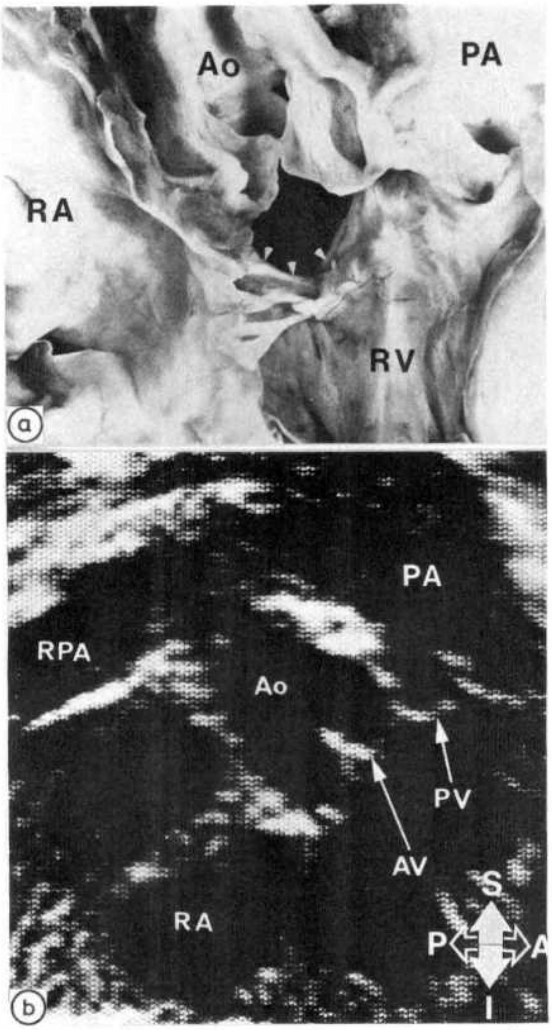

Fig 2 *(a) Photograph of the right ventricular aspect of a heart with normal connections showing a doubly committed ventricular septal defect with its superior margin formed by the arterial valves in fibrous continuity, an absent outlet septum, and a deficient subpulmonary infundibulum. (b) Subxiphoid right ventricular long axis echocardiogram in the same patient. There is no outlet septum, a fibrous continuity of the arterial valves, and deficiency of the "septal" aspect of the subpulmonary infundibulum. Arrowheads indicate the inferior rim of the ventricular septal defect. RA, right atrium; AV, aortic value; PA, pulmonary artery; RPA, right pulmonary artery. See fig 1 for other abbreviations.*

aortopulmonary raphe the associated cardiac abnormalities were consistent. Thus when the aortic valve overrode, it was the subpulmonary outflow that was obstructed and the pulmonary arteries were hypoplastic. Overriding by the pulmonary valve was associated with aortic stenosis and obstructive lesions of the aortic flow pathway (fig 3).

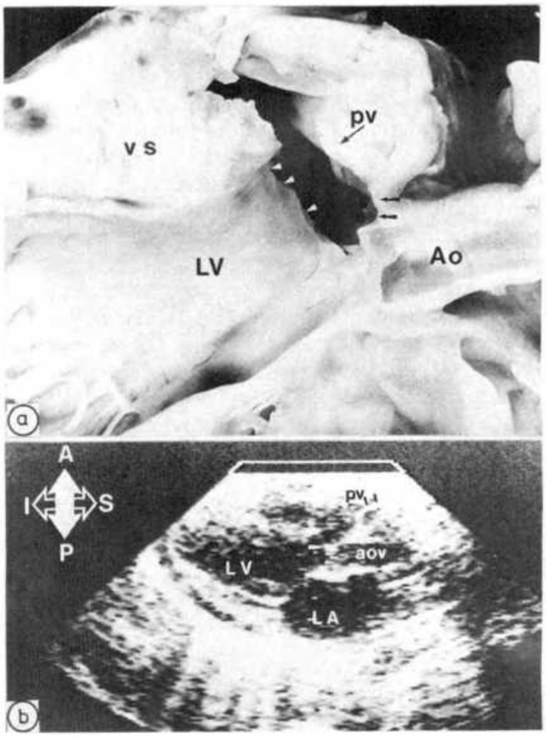

Fig 3 *(a) Long axis view of the left ventricle of a heart with interrupted aortic arch and a doubly committed subarterial defect. The lower margin of the defect is indicated by white arrowheads. The superior margin is formed by the arterial valves in continuity. The pulmonary valve overrides the septal defect and the aortic valve is bifoliate. The offsetting of the arterial valve leaflets despite fibrous continuity is shown by black arrows. (b) Long axis echocardiogram of this patient showing absent outlet septum, fibrous continuity of the arterial valves, deficient subpulmonary infundibulum, and overriding pulmonary valve. Note the offsetting of the arterial valves caused by interposition of aortic sinus. The arrowheads indicate the arterial valve leaflets. aov, aortic valve. See figs 1 and 2 for other abbreviations.*

ECHOCARDIOGRAPHIC/ANGIOCARDIOGRAPIC REVIEW

Preoperative angiographic diagnosis was available in 307 of 313 patients (261 of 265 in the first group and 46 of 48 of those with doubly committed defects). Preoperative echocardiographic diagnosis was available in 271 of 313 patients (234 of 265 in the first group and 37 of 48 of those with doubly committed defects). There were 225 of 265 patients in the first and 37 of 48 in the second group with both echocardiographic and concurrent angiographic diagnoses.

Major associated defects in those with doubly committed defects included five (10%) with complete transposition, six (13%) with double outlet

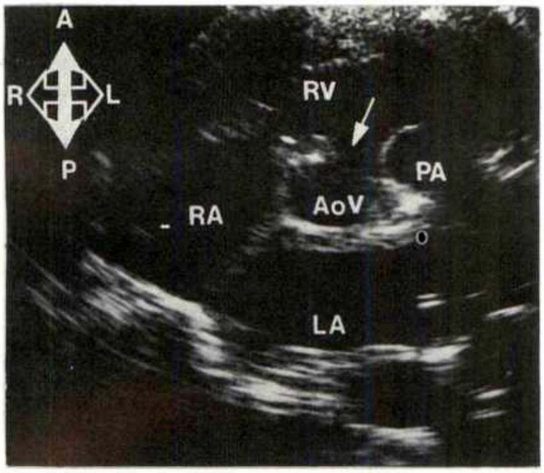

Fig 4 *Short axis echocardiogram in a patient with doubly committed subarterial ventricular septal defect (arrow). AoV, aortic valve. See figs 1 and 2 for other abbreviations.*

right ventricle, nine (19%) with overriding aortic valve and right ventricular outflow obstruction, and five (10%) with obstruction to the left ventricular outflow. The aortic valve was trifoliate in 45 (94%) and bifoliate in three (6%) patients each of whom had an abnormal aortic arch.

Echocardiographic sensitivity and specificity for prospective differentiation of doubly committed from other outlet defects were 95% and 99% respectively. There were three false positive and two false negative diagnoses. These arose from technically inadequate recordings that resulted in errors in interpretation. Retrospective analysis showed that all echocardiograms from those with doubly committed defects showed absence of the outlet septum and deficiency of the subpulmonary infundibulum. This was shown by the presence of fibrous continuity between the facing leaflets of the aortic and pulmonary valves. None the less, there was offsetting of the facing leaflets in five (14%) of 35 (fig 3), and two (6%) of 35 showed perimembranous extension of the ventricular septal defect. Best visualisation of the fibrous continuity and the outflow anatomy was obtained in 25 (71%) of 35 studies in the subxiphoid long axis view of the right ventricle (fig 2b). In six studies there were technically inadequate subxiphoid views. Parasternal long and short axes (fig 4) were the next most helpful views, particularly when there was rotation from one view to the other.[5] Prolapse of the right coronary leaflet was diagnosed in eight studies (fig 5).

Angiocardiographic sensitivity and specificity for differentiation of doubly committed from other outlet defects were 50% ($p < 0{\cdot}001$ versus echocardiography) and 97% respectively. There were 23 false negative and seven false positive diagnoses. Of 40 biplane cineangiograms available for review, left ventriculogram projections were in the long axis[1] in 37 (93%) and in the anteroposterior axis in three (7%). Unequivocal evidence of continuity of the aortic and pulmonary leaflets was established in only 19 (48%) of 40 patients. Frequently, the defect was not well defined and the position of the pulmonary valve was difficult to assess.

Aortography demonstrated prolapse of one or more aortic valve leaflets in 14 (38%) of 37 patients with ventriculoarterial concordance. In 12 there was prolapse of the right coronary leaflet and in two there was prolapse of both the right and non-coronary leaflets. There was aortic regurgitation in 11 (79%) of 14 but this was not present before the age of 2·3 years. Aortic regurgitation did not occur in any patient who did not have aortic leaflet prolapse.

Discussion

MORPHOLOGY

Previous description of doubly committed subarterial defects presumed that the normal outlet septum was the muscle mass extending beyond the tricuspid valve up to the pulmonary valve.[1] The criterion for diagnosis was the absence of the "outlet septum" as thus defined, with the defect being roofed by the leaflets of the aortic and pulmonary valves in fibrous continuity.[6 7] This study shows that more detailed analysis of the right ventricular outflow tract

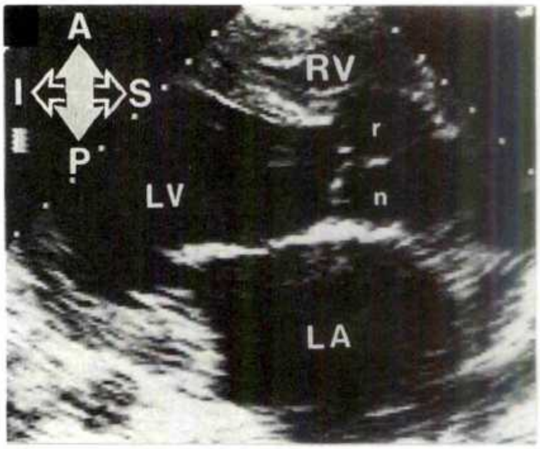

Fig 5 *Parasternal long axis echocardiogram in a patient with an isolated doubly committed subarterial defect and prolapse of the right coronary aortic leaflet. The leaflet is prolapsed through the defect into the right ventricular outflow tract. n, non-coronary leaflet; r, right coronary leaflet. See figs 1 to 4 for other abbreviations.*

is needed before the morphology of the doubly committed defect can be understood.

In the normal heart, the true outlet septum, that portion of muscle interposing between the outflow component of the left and right ventricles cephalad to the tricuspid valve, is small. More importantly, there is a sleeve of subpulmonary infundibulum which supports the leaflets of the pulmonary valve, yet separates the right ventricular outflow tract from the outside of the heart rather than from the cavity of the left ventricle. This arrangement produces the normal offsetting between the leaflets of the aortic and pulmonary valves. Presence of a doubly committed defect, therefore is based not only on absence of the septum but also on absence of the "septal" aspect of the subpulmonary infundibulum. It is only in these circumstances that the leaflets of the aortic and pulmonary valves are seen in fibrous continuity. Offsetting of the aortic and pulmonary valves can still occur when there is a doubly committed defect in the absence of the subpulmonary infundibulum. This occurs when the wall of an arterial sinus is interposed between the valves. This anatomical feature was recently described[2] and is endorsed by our findings. The morphological criteria suggested above for the recognition of a doubly committed defect hold good irrespective of the ventriculoarterial connection.

VENTRICULAR OUTFLOW OBSTRUCTION

"Fallot's tetralogy" is often described as occurring with doubly committed subarterial ventricular septal defect.[8 9] The morphology of tetralogy, however, includes an outlet malalignment ventricular septal defect, overriding of the aortic valve, and subpulmonary infundibular narrowing. If we chose a single morphological criterion for the tetralogy of Fallot it would be anterocephalad deviation of the septal insertion of the muscular outlet septum. In doubly committed subarterial defects, the outlet septum is absent and the subpulmonary infundibulum incomplete; thus there is shortening of the narrowed right ventricular outflow tract and, indeed, obliteration of its "septal" aspect. Therefore, coexistence of Fallot's tetralogy, as defined, and a doubly committed defect is not tenable. This is, of course, dependent upon the definition chosen. None the less, we submit that the description of overriding of the aortic valve in the presence of aortic-pulmonary valvar continuity and obstruction of the pulmonary outflow tract is a more accurate definition of doubly committed subarterial ventricular septal defect in association with obstruction of the pulmonary outflow tract.

Our pathological review has shown that restriction of the right or left ventricular outflow tracts is associated with displacement of the fibrous raphe between the aortic and pulmonary valves along with overriding of the unobstructed valve. In addition, there may be thickening or dysplasia of the leaflets of the arterial valves and accessory tissue adherent to them or any combination of these features. The major associated abnormalities reflect the haemodynamic consequences of the presence of outflow tract obstruction. Our findings may explain why subvalvar obstruction occurs after patch repair in cases with overriding arterial valves.[8]

CLINICAL IMPLICATIONS

Cross sectional echocardiography is more sensitive than axial cineangiography in the diagnosis of the doubly committed defect. Echocardiography offers a wide variety of views of interest, allowing investigation of the ventricular septum, outflow tracts, and associated anomalies. Since 1984, some patients with isolated doubly committed defects have undergone corrective surgery without preoperative angiography.[10] Angiography none the less remains helpful in more closely defining abnormalities of the aortic valve, pulmonary arteries, and aortic arch.

Conclusion

This study challenges the presently accepted concept of the "outlet septum" in the normal heart and expands the definition of the doubly committed subarterial defect. The diagnosis requires an incomplete subpulmonary infundibulum as well as absence of the outlet septum and fibrous continuity of the aortic and pulmonary valves. These features are more readily demonstrated by echocardiography than by angiography. This information facilitates planning of surgical strategy. Closure of the isolated doubly committed defect can usually be performed through the pulmonary artery with low morbidity, even in small infants, without the need for invasive investigation.[10]

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Correlations of lung morphology, pulmonary vascular resistance, and outcome in children with congenital heart disease

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SUMMARY Pulmonary vascular resistance was measured in air, oxygen, and after administration of vasodilators in 14 children with pulmonary hypertension and congenital heart disease. Lung morphology was examined by light microscopy and assessed quantitatively. In this selected group of patients (*a*) medial muscle thickness of $>20\%$ in the intra-acinar arteries and Heath-Edwards changes of I or II were significantly associated with perioperative death from pulmonary complications after cardiac surgery; (*b*) children with lower percentage medial muscle thickness had a higher baseline resistance ($r = -0{\cdot}84$) associated with Heath-Edwards grade III or higher changes (most of these patients were not offered corrective sugery); (*c*) when the lowest pulmonary vascular resistance was <3 units, Heath-Edwards grading was I or II ($n = 4$). When the pulmonary vascular resistance was >6 units, however, there was no direct correlation with Heath-Edwards grading ($n = 9$). Four patients with a resistance of >6 units had only grade I or II changes. Three had a medial muscle thickness above 20%, and were among those who died at or soon after operation.

It is concluded that (*a*) patients with a lowest pulmonary vascular resistance of >6 units have a bad prognosis whatever their lung morphology; and (*b*) some patients with Heath-Edwards grade I or II will have a high resistance (this group has a high medial muscle mass and a poor prognosis and would not be detected by Heath-Edwards grading alone).

Many congenital heart defects can be corrected surgically during childhood, but the timing of operation is important because progressive damage to the pulmonary circulation may make anatomical correction impossible. Many techniques have been used to assess pulmonary circulatory damage, including assessment of haemodynamic function,[1 2] pulmonary wedge angiography,[3] and lung biopsy.[4-6] The purpose of this study was to try to define the relation between lung morphology, measurements of pulmonary vascular resistance, and outcome.

Patients and methods

PATIENTS

At the Brompton Hospital pulmonary vascular resistance in air and 100% oxygen is measured in children with suspected pulmonary vascular disease. Those with resistances of between 4 and 10 Wood Units ($\text{mm Hg.l}^{-1}\text{.min.m}^2$) have a lung biopsy. Biopsy is also performed if there are clinical grounds to doubt the feasibility of operation. We have reviewed 14 patients studied over a seven year period in whom full physiological and histological data are available. Table 1 gives their details and diagnoses. Lung tissue was obtained at biopsy ($n = 9$) or necropsy ($n = 5$). Informed consent was obtained for all procedures, usually from the parents, and all research protocols were approved by the Brompton Hospital Ethics Committee.

METHODS

Measurement of pulmonary vascular resistance

Pulmonary vascular resistance was calculated from pulmonary blood flow measured by the direct Fick principle. Oxygen consumption was measured by mass spectrometry. Full details of the method have been published.[7 8] Measurements were usually made

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Table 1 *Details and diagnoses of patients studied (arranged in ascending order of baseline pulmonary vascular resistance)*

No	*Sex*	*Height (centile)*	*Weight (centile)*	*Diagnosis*	*Age at first catheter*	*Age at lung biopsy/necropsy*
1	F	< 3	< 3	AVSD, PDA, DS	13 mnth	13 mnth
2	M	10	< 3	VSD, DS	9 mnth	9 mnth
3	M	3	< 3	DORV, MA	10 yr 10 mnth	10 yr 11 mnth
4	F	< 3	< 3	VSD, PDA, PAB, C	5 mnth	6 mnth
5	M	10	25	AVSD, DS	3 yr 4 mnth	3 yr 4 mnth
6	F	25	30	VSD	7 yr 8 mnth	7 yr 8 mnth
7	M	< 3	< 3	VSD, PDA, PAB, C	2 mnth	2 mnth
8	F	< 3	3	VSD, PDA, C	15 mnth	18 mnth
9	F	50	50	TGA, VSD, PAB	2 yr 5 mnth	2 yr 5 mnth
10	M	35	< 3	LVOTO, MS, EFE	13 mnth	13 mnth
11	F	30	30	ASD (S)	19 yr 4 mnth	19 yr 2 mnth
12	F	80	60	ASD (S)	2 yr 3 mnth	2 yr 3 mnth
13	F	< 3	< 3	AVSD, MR	16 mnth	16 mnth
14	F	3	< 3	VSD	8 yr 8 mnth	12 yr 4 mnth

ASD(S), ostium secundum atrial septal defect, AVSD, atrioventricular septal defect; C, coarctation; DORV, double outlet right ventricle, DS, Down's syndrome; EFE, endocardial fibroelastosis; LVOTO, left ventricular outflow tract obstruction, MA, mitral atresia; MR, mitral regurgitation, MS, mitral stenosis; PAB, pulmonary artery banding, PDA, patent arterial duct; TGA, transposition of great arteries; VSD, ventricular septal defect.

with the patients ventilated both on air and 100% oxygen. When necessary epoprostenol (prostacyclin) was given by continuous intravenous infusion at rates of 5–20 ng/kg/min[9] and a bolus of tolazoline (1–2 mg/kg) was given into the pulmonary artery.[10]

Assessment of lung morphology

The lung tissue was reviewed without knowledge of the clinical details or resistance measurements. The abnormalities were graded according to the Heath-Edwards classification,[4] modified to include the predilatation phase.[11-13] For the quantitative studies, the mean number of arteries measured in each specimen was 35, range 20–55. The mean percentage arterial medial thickness was calculated and compared with the normal values for age[6] by non-orthogonal analysis of variance. The normal values were derived from non-injected, postmortem material. The mean external diameter and muscularity of the arteries accompanying the different airway generations was determined and compared with age matched controls. The ratio of patent intra-acinar arteries to alveoli was calculated to compensate for differences in the degree of inflation in different lungs. The alveolar/arterial ratio was not determined in specimens showing generalised arterial dilatation.

Results

PULMONARY VASCULAR RESISTANCE MEASUREMENTS

Table 2 summarises the haemodynamic data. The group mean baseline pulmonary blood flow was 5·9 l/min/m² (range 0·6—14·0) and mean pulmonary vascular resistance was 10·1 Wood units (range 2·1—24·6). Even in patients with high pulmonary vascular resistances, 100% oxygen, epoprostenol, or tolazoline produced vasodilatation. This was usually

Table 2 *Mean pulmonay artery pressure (PAP, mm Hg), pulmonary blood flow (Qp, l/min/m²), and pulmonary vascular resistance (PVR, mm Hg.l⁻¹.min.m²)*

	Baseline			*100% oxygen*			*Drug*			
Case	*PAP*	*Qp*	*PVR*	*PAP*	*Qp*	*PVR*	*PAP*	*Qp*	*PVR*	*Drug used*
1	35	14·0	2·1	—	—	—	—	—	—	—
2	28	10·3	2·2	24	9·0	2·1	—	—	—	—
3	51	12·3	3·0	50	10·0	3·7	—	—	—	—
4	25	4·4	3·2	22	5·2	2·1	20	6·8	1·3	O_2/PGI_2
5	62	7·6	7·2	61	6·8	7·8	46	6·8	5·5	O_2/PGI_2
6	78	6·9	9·8	85	7·0	10·5	80	8·2	8·4	PGI_2
7	14	0·6	11·6	29	1·9	10·2	28	2·3	7·8	O_2/PGI_2
8	40	2·7	11·9	34	3·8	6·6	—	—	—	—
9	33	2·4	11·9	37	2·8	11·3	32	3·0	9·2	O_2/PGI_2
10	—	—	—	50	2·9	11·9	45	4·1	7·3	O_2/PGI_2
11	60	3·9	14·2	58	5·0	10·8	58	6·5	8·4	O_2/PGI_2
12	60	2·9	18·9	56	4·9	10·4	—	—	—	—
13	—	—	—	40	1·7	22·0	—	—	—	—
14	86	3·3	24·6	86	4·2	19·3	—	—	—	—

O_2, 100% oxygen; PGI_2, epoprostenol (prostacyclin).

Table 3 *Pathological findings*

			Intra-acinar arteries				
No	*Tissue*	*Preacinar IP/IF*	*Ext/Dil*	*% MWT**	*Size*	*No†*	*Grade PVD*
1	PM	+	Ext	24‡	N	—	I–II
2	PM	+	Ext	36‡	I	6 1	II
3	LB	O	Ext	26‡	D	16	I–II
4	LB	O	Ext	30‡	N	9 1	I
5	LB	+	Ext	20‡	I	10 5	III
6	LB	+	Ext	22‡	D	9 8	III late
7	LB	+	Ext	15‡	I	—	II
8	LB	+	Dil	10	I	8	III predil
9	LB	+	Ext ± Dil ±	13	N	6	III predil
10	PM	O	Ext	37‡	N	9 2	I–II
11	LB	O	Ext	8	N	10	II
12	PM	+	Dil	6	N	9 6	III predil
13	LB	O	Ext	37*	D	—	I–II
14	PM	+ plex	Dil	11	—	—	IV

*Normal mean value 7·4. †Normal range 8 2–11 2
‡Significantly greater than normal.
LB, lung biopsy; PM, lung tissue obtained at necropsy; predil, pre-dilatation; IP/IF, intimal proliferation/fibrosis; % MWT, percentage arterial medial thickness in arteries 50–100 μm in diameter; grade PVD, grade of pulmonary vascular disease, D, decreased; I, increased; O, not available, Ext, extension of arterial medial thickness into more peripheral arteries than normal; Dil, dilatation; plex, plexiform lesions.

manifested by an increase in flow with unchanged pulmonary artery pressure. The mean fall in pulmonary vascular resistance with 100% oxygen was 2·2 units (range −0·7 to 5 3, $p < 0{\cdot}02$, $n = 11$) and the mean additional fall in resistance with a bloodborne vasodilator was 2·3 units (range 0·8 to 4·3, $p < 0{\cdot}001$, $n = 10$).

LUNG MORPHOLOGY

All 14 patients showed an increase in pre-acinar (proximal to the respiratory unit) arterial medial thickness and ten showed extension of muscle into more peripheral arteries than normal. In nine of the ten patients this was associated with a significant increase in intra-acinar percentage arterial medial thickness (table 3). The four patients who did not show this extension did not have an increase in intra-acinar medial thickness and the intra-acinar arteries appeared to be dilated. In these cases the structural abnormalities present in both the pre- and intra-acinar arteries were characteristic of grade IV pulmonary vascular disease ($n = 1$) (Heath-Edwards) or of the predilatation phase ($n = 3$).[11-13] In three children there was a reduction in the mean external diameter of the arteries accompanying respiratory bronchioli. In two patients this reduction in intra-acinar size was probably accounted for by their small body size for age. Only case 3 had an abnormally high alveolar/arterial ratio, indicating a reduction in the number of intra-acinar arteries.

CORRELATION OF HAEMODYNAMIC AND MORPHOMETRIC DATA

Pulmonary vascular resistance measured when the patients were breathing air (baseline pulmonary vascular resistance) was lowest in those with the greatest percentage arterial medial thickness (AMT) in arteries that were 50–100 μm in diameter (pulmonary vascular resistance = $-0{\cdot}60.\text{AMT} + 21{\cdot}5$, $r = -0\ 84$, $p < 0{\cdot}002$, fig 1). The fall in pulmonary vascular resistance when vasodilators were given (baseline minus lowest pulmonary vascular resistance) was greatest in those with the highest resistances, and hence in those who had the lowest percentage arterial medial thickness (change

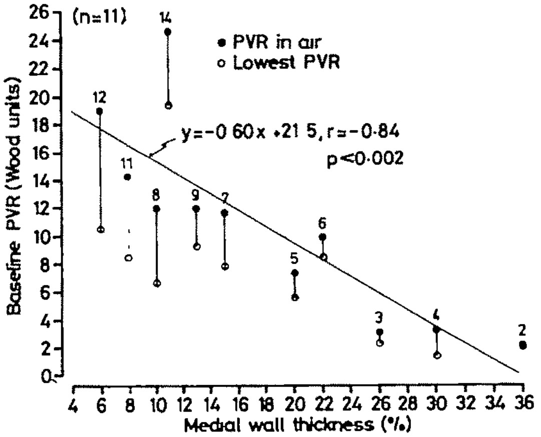

Fig 1 *Medial wall thickness of intra-acinar arteries plotted against pulmonary vascular resistance (PVR). The figure is based on the 11 patients for whom data on baseline PVR, and fall in PVR after vasodilators (reversibility) are shown. The line is the regression of baseline resistance on medial wall thickness. The numbers identify the patients.*

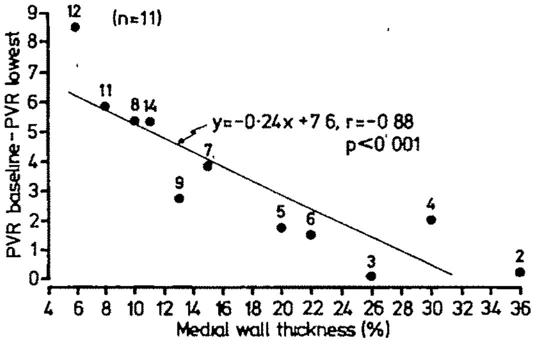

Fig 2 *Medial wall thickness of intra-acinar arteries plotted against change in pulmonary vascular resistance (PVR baseline—PVR lowest). The figure is based on the 11 patients for whom baseline and reversibility data are available. The numbers identify the patients.*

in pulmonary vascular resistance = −0·24.AMT + 7·6, r = −0·88, p < 0·001, fig 2). Pulmonary blood flow was highest in those with the greatest percentage arterial medial thickness (flow = 0·27.AMT + 0·38, r = 0·72, p < 0·02, fig 3). Change in blood flow (highest minus baseline) did not correlate with medial muscle thickness (fig 4). No haemodynamic measurement correlated with the number of intra-acinar arteries.

Figure 5 shows the relation between baseline and lowest pulmonary vascular resistance and the histological grading of the biopsy specimens by the modified Heath-Edwards classification. A lowest pulmonary vascular resistance of <3 units was associated with grade I or II changes (n = 4). The single case with early grade III changes had a lowest resistance of 5·5 units. When the resistance was >6 units there was no correlation with the Heath-Edwards classification. Five patients had disease that was late grade III or worse, and in the remaining four cases the pulmonary vascular abnormalities were less severe (grade I/II) than expected.

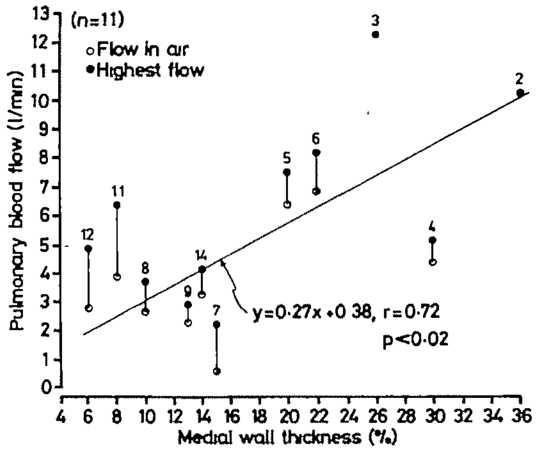

Fig 3 *Medial wall thickness of intra-acinar arteries plotted against pulmonary blood flow. The figure is based on the 11 patients for whom baseline and reversibility data are available. The line is the regression of baseline flow on medial wall thickness. The numbers identify the patients.*

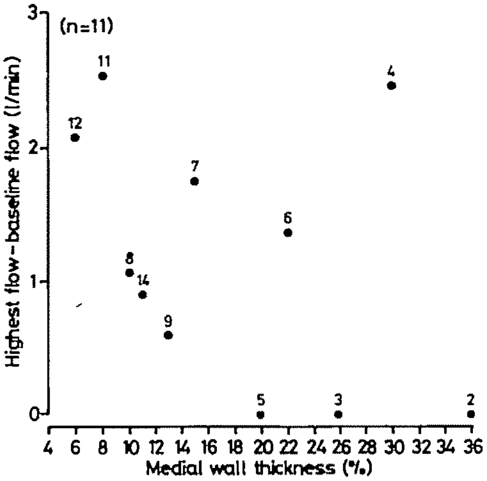

Fig 4 *Medial wall thickness of intra-acinar arteries plotted against change in pulmonary blood flow (highest minus baseline). The figure is based on the 11 patients for whom baseline and reversibility data are available. The numbers identify the patients.*

OUTCOME

Six of seven patients in whom corrective cardiac surgery was attempted died within a week of operation (cases 1–3, 5, 10, and 12). Child 13 died within hours of his lung biopsy. The notes were reviewed retrospectively without knowledge of the resistance or morphometric measurements. Pulmonary vasoconstriction or structural pulmonary vascular disease were considered to be major factors contributing to all the deaths. The only physiological or histological measurement that was predictive of perioperative death was an arterial medial thickness of ⩾20% (p < 0·05, Fisher's exact probability test, one tailed). Of the other six patients, two died of progressive right heart failure (patients 7 and 14). Patients 4 and 6 remain well two years after investigation. Patient 8 had ligation of the arterial duct and repair of coarctation: the ventricular septal defects were left open, but subsequently closed spontaneously, and she remains well. Patient 9 had a palliative Mustard's procedure without closure of the ventricular septal defects; she is well but becomes cyanosed on exertion.

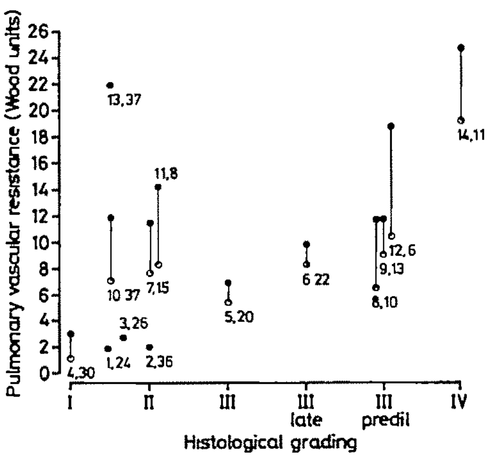

Fig 5 *Heath-Edwards grading, modified to include the predilatation phase (III predil) plotted against pulmonary vascular resistance. The numbers are the patient number and the medial wall thickness of intra-acinar arteries (%) respectively.* ●, *baseline resistance;* ○, *lowest resistance.*

Discussion

These patients represent a highly selected group, varying in age, type of cardiac anomaly, and severity of pulmonary vascular disease. The proportion of patients with a pulmonary vascular resistance of at least 5·5 units (10/14) and coming to necropsy (5/14) indicates that the severe disease/high risk end of the spectrum is overrepresented in this series. Outcome was not an independent variable, because management was based on the interpretation of the data available at the time. We report these patients because we have both accurate measurements of pulmonary vascular resistance and reactivity as well as detailed lung morphology.

Measurement of pulmonary blood flow by the direct Fick principle depends on direct measurement of oxygen consumption. Many investigators, however, rely on tables of predicted values, which are unreliable.[14 15] It is also important to distinguish fixed anatomical damage from reversible pulmonary vasoconstriction, otherwise the child may be denied a potentially curative operation. We routinely use at least one of 100% oxygen, epoprostenol, and tolazoline as pulmonary vasodilators when the resistance is raised. Details of interactions between these agents can be found elsewhere.[9 10]

We compared measurements of percentage arterial medial thickness with outcome after cardiac surgery. In the immediate postoperative period six died of pulmonary circulatory disease. A percentage arterial medial thickness of >20% was associated with perioperative death after cardiac surgery ($p < 0.05$). This confirms the findings of others.[9 11] Patients with only slightly increased medial thickness had associated grade III or worse Heath-Edwards changes, and most were not offered corrective surgery. The only death after lung biopsy (case 13) was in the infant with the highest percentage arterial medial thickness. Perhaps even minor surgical procedures carry an increased risk if the percentage arterial medial thickness is high.

Despite this, baseline pulmonary vascular resistance showed a negative correlation with percentage arterial medial thickness (fig 1) and baseline flow a slightly less good positive correlation (fig 3) in the 11 patients in whom baseline pulmonary vascular resistance and pulmonary vascular resistance after vasodilators had been given were known. This relation has been described before.[9 16] The better agreement reported here is probably because pulmonary blood flow was measured directly rather than estimated from assumed values of oxygen consumption. It may seem surprising that a high resistance is associated with normal or only mildly increased arterial medial wall thickness. Serial reconstruction studies in other patients, however, have shown high resistance to be caused by associated severe proximal obstruction.[11 17] It is likely that smooth muscle regresses as flow and pressure drop distal to such obstructions—this is analagous to the regression of smooth muscle distal to a surgically placed pulmonary artery band.

We have also shown that patients with normal or only modestly increased arterial medial muscle and high resistances show a much greater absolute drop in resistance when they are given vasodilators than those with greatly increased arterial muscle and normal or only modestly increased resistance (fig 2). It seems paradoxical that the less arterial muscle present, the greater the reversibility. If resistance is determined by very narrow proximal vessels, however, even a small percentage increase in the lumens of such vessels will reduce resistance considerably. When there is increased muscle in distal vessels, the pulmonary vascular resistance is lower than when the obstruction is more proximal, leaving less scope for a fall in resistance with vasodilators.

We also looked at the relation between lowest pulmonary vascular resistance and the modified Heath-Edwards grading (fig 5). The Heath-Edwards classification does not include a pre-dilatation phase, which is therefore likely to be misdiagnosed as grade II or early grade III. If this phase is omitted, the agreement between pulmonary vascular resistance and grading is less good. The high resistances measured in three patients independently classified as being in the pre-dilatation phase by histological grading supports the view that this phase is a clinically important addition to the Heath-Edwards classification. The finding of inoperable pulmonary vascular disease in patients with resistances as low as 6 units is surprising, since much higher values have been reported as compatible with operability.[1 2] These values may be higher because of failure to measure pulmonary vascular resistance accurately because oxygen consumption was only assumed. Another factor may be failure to administer appropriate vasodilators. In doubtful cases it is important to administer both 100% oxygen and a bloodborne agent to determine the lowest pulmonary vascular resistance.[9 10]

In four of 14 cases the pulmonary vascular resistance was higher than expected from the histological grading. It is thus difficult to know how to manage patients with a lowest resistance of >6 units, in whom there is no correlation between measured resistance and Heath-Edwards grading. Some will have inoperable pulmonary vascular disease, whereas others will have an apparently benign histological examination. Of the four patients in this latter group, patient 13 died after a lung biopsy, patient 10 died soon after corrective surgery, and patient 7 died of progressive cardiorespiratory failure several months after palliative operation. These three patients had an increased arterial medial thickness, which may not always permit successful operation.[11] The fourth patient had an isolated atrial septal defect closed without complications, and clinically her pulmonary hypertension has regressed, but she has not been recatheterised. The data suggest that there is a group of patients with a high resistance, an apparently benign histological picture, and a poor prognosis. This group is missed if lung biopsy specimens are classified by the Heath-Edwards grading alone.

It could be argued that because of the poor prognosis patients with a lowest resistance of >6 units should not be offered operation irrespective of the lung histology. None the less, if it is decided that such patients should have an operation, a lung biopsy would need to be performed in all children with a resistance of >6 units to distinguish the "benign" group from those with disease that is late grade III or worse, who by any criteria are inoperable. Many patients in this "benign" group need to be studied to see whether they really should be offered corrective operation.

Any conclusions based on a selected series of this diversity must be tentative. Many children with congenital heart disease have a low pulmonary vascular resistance, never have a lung biopsy, and have a smooth postoperative course. In children in whom pulmonary vascular disease is suspected clinically, however, accurate measurement of pulmonary vascular resistance, combined in certain cases with lung biopsy, gives essential information for rational decision making.

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Cardiomyopathy in the Kearns-Sayre syndrome

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SUMMARY The Kearns-Sayre syndrome is a mitochondrial myopathy characterised by ptosis, chronic progressive external ophthalmoplegia, abnormal retinal pigmentation, and cardiac conduction defects. A unique case is reported in which there was rapid development of progressive congestive cardiac failure that required cardiac transplantation.

A review of published reports of mitochondrial myopathy shows that a minority of cases (< 20%) have cardiac involvement. This had previously been limited to abnormalities of cardiac conduction with progressive heart block. Myocardial biopsy has, however, shown ultrastructural evidence of a generalised mitochondrial disorder which hitherto has not been associated with a functional deficit.

The association of external ophthalmoplegia, abnormal retinal pigmentation, and complete heart block was first reported by Kearns and Sayre in 1958,[1] although Sandifer had already described a case of bundle branch block in association with external ophthalmoplegia.[2] The high risk of sudden death from the cardiac conduction defect in this syndrome has become less important with the development of implantable pacemakers, and prolonged survival has been reported.[3] The aetiology of the condition is unknown but the pathology has only recently been elucidated.

Several early necropsy studies did not show any specific abnormality of the myocardium.[1 4] Endomyocardial biopsy also showed non-specific changes—for example, interstitial fibrosis and hypertrophy[5] on light microscopy. Only on electron microscopy has any specific abnormality been detected, namely glycogen accumulation and proliferation of abnormal mitochondria.[3 5] It is now recognised that the Kearns-Sayre syndrome forms part of a heterogeneous group of mitochondrial cytopathies.[6 7]

Although abnormalities of myocardial ultrastructure have been found in the Kearns-Sayre syndrome these have not been associated with myocardial dysfunction. We report a patient with Kearns-Sayre syndrome who presented with congestive cardiac failure caused by dilated cardiomyopathy which was so severe that heart transplantation was required.

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Case report

INITIAL PRESENTATION

A 21 year old man presented with a two month history of dry cough and progressive dyspnoea. At the time of admission he became breathless when he climbed a single flight of stairs and he was orthopnoeic. He did not have chest pain. There was no history of a preceding influenza-like illness. In the past he had had bilateral ptosis surgically corrected when he was 16 years old and had been investigated for abnormal retinal pigmentation (visual evoked responses and electroretinograms were normal).

He smoked 20 cigarettes a day and drank about 20 pints of beer a week. He had two siblings who were well and there was no family history of note.

He was plump and normally developed. The pulse rate was 100 beats/minute with frequent extrasystoles, and the blood pressure was 110/80 mm Hg. The jugular venous pressure was grossly elevated to the level of his pinna and did not fall on inspiration. The apex was readily palpable in the 6th intercostal space in the anterior axillary line, and auscultation showed normal heart sounds. There was palpable hepatomegaly. Chest and neurological examination appeared normal. Fundal examination showed abnormal pigmentation around the macula (fig 1).

INVESTIGATIONS

Full blood count, blood sugar, thyroid function tests, and concentrations of fasting lipids, serum urea, and electrolytes were all normal. Antinuclear factor and rheumatoid factor were negative. The concentration of serum bilirubin was increased at 27 mmol/l (normal < 17 mmol/l), as was aspartate aminotrans-

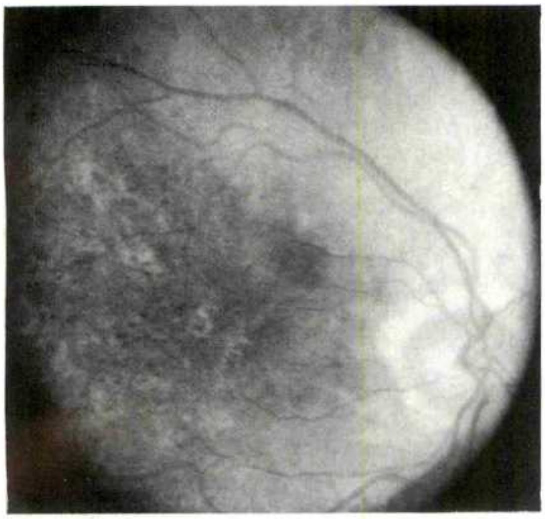

Fig 1 *Retinal photograph showing the typical "salt and pepper" retinal pigmentation of mitochondrial myopathy.*

ferase activity at 41 units/l (normal 6–35 units/l). Alkaline phosphatase activity was normal. Chest *x* ray showed pulmonary oedema with cardiomegaly (cardiothoracic ratio 17·8/30·6). The electrocardiogram showed sinus tachycardia with ventricular extrasystoles and left axis deviation. Echocardiography showed biventricular dilatation and generalised poor function, but all the valves appeared to be normal. The isotope ventriculogram gave a calculated ejection fraction for the right ventricle of 15% and 17% for the left ventricle. Twenty four hour ambulatory electrocardiography showed frequent ventricular extrasystoles and technical ventricular tachycardia (runs of three consecutive extrasystoles).

COURSE

A diagnosis of dilated cardiomyopathy was made and he was treated with diuretics, enalapril, warfarin, and amiodarone. On this regimen the pulmonary oedema cleared and he became less breathless. Two months later, however, he deteriorated and was readmitted with increasing dyspnoea, cough productive of pink frothy sputum, and lethargy. He had four pillow orthopnoea. On examination he was in severe congestive cardiac failure with bilateral pitting ankle oedema, high venous pressure, sinus tachycardia, and gallop rhythm.

Cardiac catheterisation at this time showed raised right heart pressures with mean right atrial pressure of 24 mm Hg. Right ventricular pressure was 60/30 and pulmonary artery pressure was 60/40 (mean of 45 mm Hg). Pulmonary wedge pressure was 38 mm Hg and left ventricular pressure was 78/30. Cardiac output was 2·9 l/min. During the catheterisation a 2:1

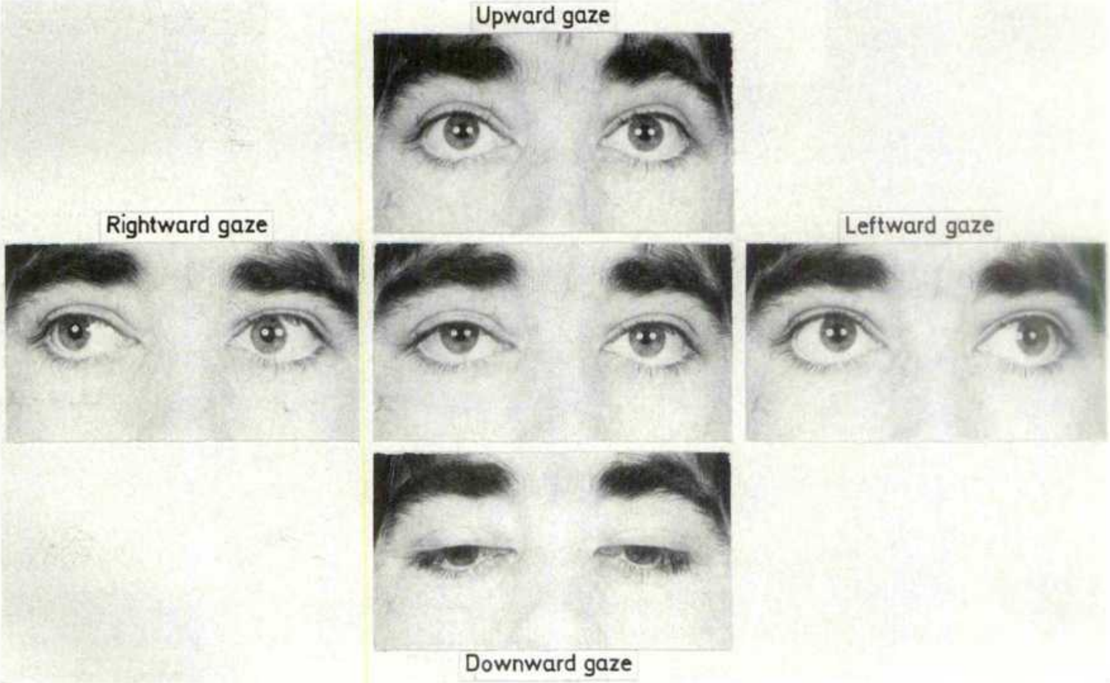

Fig 2 *Limitation in the extent of eye movements by external ophthalmoplegia.*

atrioventricular block developed. During this second admission his voice weakened and a bovine cough developed. Indirect laryngoscopy showed a paralysed left vocal cord which raised the possibility of Ortner's syndrome.

He was transferred to Harefield Hospital where an urgent heart transplantation was performed. He had a postoperative course complicated by a cardiac arrest, status epilepticus, and he required artificial ventilation for about 10 days. He gradually recovered and ten weeks after the transplantation he was transferred back to Bristol for rehabilitation.

On readmission there was considerable distal wasting of the hands, forearms, and legs with contractures of both achilles tendons. He had ophthalmoplegia and weak sternomastoids. His cardiovascular state was satisfactory with no signs of heart failure.

The history of corrected ptosis and finding of abnormal retinal pigmentation with the development of ophthalmoplegia and skeletal myopathy led to the diagnosis of the Kearns-Sayre syndrome.

NEUROLOGICAL INVESTIGATIONS

Electroencephalography was abnormal with a generalised excess of very slow wave activity particularly over the left hemisphere. There were occasional sharp wave discharges suggestive of a liability to seizures. Computed axial tomography of the brain showed no midline shift and no focal changes. The ventricular system showed mild dilatation. Nerve conduction studies showed normal motor and sensory velocities and normal amplitudes of evoked motor potentials apart from those muscles which had atrophied completely. Electromyographic sampling showed generalised and diffuse non-specific abnormalities with loss of interference patterns related to the number of units that had atrophied within the muscles.

On review 12 months after cardiac transplantation he was fully independent without dyspnoea on exertion. He had a persistent right foot drop and weakness of dorsiflexion of the left foot. There was persistent wasting of calf muscles bilaterally. There

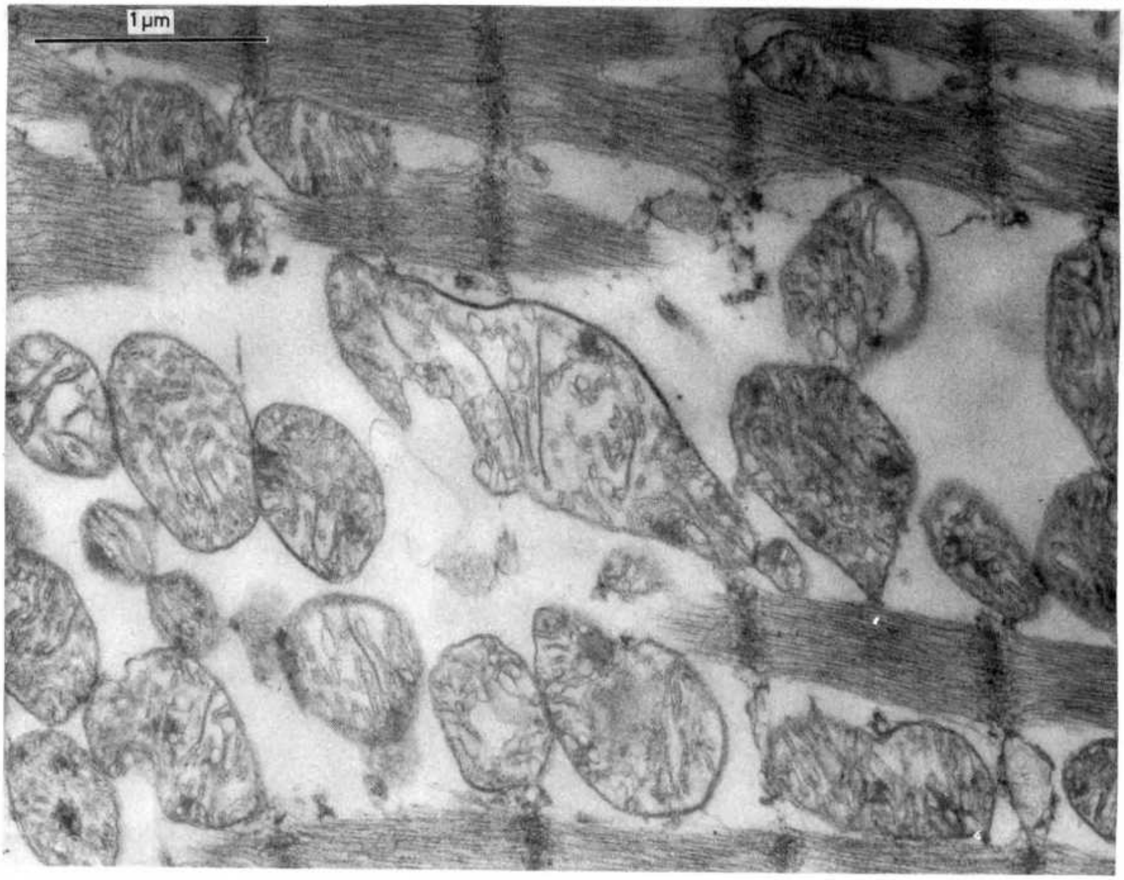

Fig 3 *Electron photomicrograph of myocardial biopsy specimen showing large numbers of abnormal mitochondria. The mitochondria are large, vacuolated, and contain electron densities.*

was weakness and wasting of the intrinsic hand muscles and wasting of the forearm muscles but no clinical weakness. Eye movements were markedly impaired (fig 2). All the reflexes were present.

HISTOPATHOLOGY

The excised heart weighed 500 g without the upper atria. The ventricular cavities were dilated and there was adherent thrombus at the apices. The specimen was fixed routinely in formol saline and processed for both histological and ultrastructural examination. Light microscopy of the myocardium showed degeneration of myocardial fibres with perinuclear vacuolation and nuclear pleomorphism and enlargement. There was diffuse and focal interstitial fibrosis that was particularly noticeable in the subendocardial region. Although these features were present in both ventricles the left ventricle showed the most severe changes. Foci of myofibrillar degeneration were also noted as demonstrated by trichrome staining. There were no features of an active myocarditis. Electron microscopy showed no significant abnormality of the myofibrils but showed various mitochondrial abnormalities. Mitochondria were increased in number but in addition were of varying size and shape, with giant mitochondria measuring up to 1·8 μm in diameter. Within the mitochondria there were electron dense areas and vacuoles (fig 3). In many the cristae were disrupted.

Discussion

The Kearns-Sayre syndrome is characterised by the triad of chronic progressive external ophthalmoplegia, abnormal retinal pigmentation, and cardiac conduction defects and is part of a heterogenous group of mitochondrial myopathies. The first of these myopathies was described by Luft *et al* in 1962[8] and they are all characterised by abnormal muscle mitochondrial morphology on electron microscopy. Recently attempts have been made to separate different clinical syndromes, for example myoclonus epilepsy with ragged red fibres (MERRF) and mitochondrial myopathy/encephalopathy, lactic acidosis, and stroke-like episodes (MELAS),[6,9] but there is no association with either specific morphological changes or mitochondrial enzyme abnormalities.[7]

In the biggest published series of patients, from one centre, with mitochondrial myopathy defined by muscle biopsy, 40 (61%) of 66 cases presented before age 20 years and the commonest presentation was ptosis in 37 (56%) often with chronic progressive external ophthalmoplegia, which ultimately affected 48 (73%) of cases.[7] Many cases (47 (71%)) also had proximal limb weakness or easy fatigue, often with absent reflexes but occasionally with extensor plantar responses. Abnormal retinal pigmentation occurred in 24 (36%) and was usually of a "salt and pepper" appearance and without associated visual defect. Sensorineural deafness occurred in 17 (26%) and important central nervous system disease with cerebellar ataxia or dementia in 18 (27%). Similar frequencies of abnormalities have been reported in cumulative series culled from published reports.[10,11] Our case is typical in that onset was before the age of 20 years with ptosis and "salt and pepper" retinal pigmentation. Neither external ophthalmoplegia nor skeletal muscle weakness was noticeable before cardiac surgery but these are often mild and ignored by the patient.[7] After his complicated postoperative course the skeletal abnormalities and ophthalmoplegia became obvious.

Cardiac function in the Kearns-Sayre syndrome as assessed clinically[7] and by haemodynamic[3,5] and imaging techniques has always previously been shown to be normal. Indeed, cardiac involvement in mitochondrial myopathies has hitherto been limited almost exclusively to the conducting tissue (though the development of cardiomyopathy has been forecast as a consequence of prolonged longevity resulting from pacing).[3] Of the 66 cases from the National Hospital of Nervous Diseases, 11 (17%) had electrocardiographic abnormalities without overt myocardial dysfunction.[7] These included in 11 cases, non-specific ST segment or T wave abnormalites (often T wave flattening),[9] and in nine cases conduction defects ranging from pre-excitation syndrome in one, first degree heart block (two cases), non-specific intraventricular conduction defects (two cases), right bundle branch block (three cases), and complete heart block (one case). Two patients had permanent pacemakers. In our case, the electrocardiogram was abnormal before transplantation with left axis deviation indicative of left anterior hemiblock and transient second degree atrioventricular block. Progressive heart block from left anterior hemiblock to symptomatic complete heart block over a seven year period has been documented[3] and prophylactic pacing has been advocated for patients with the syndrome and evidence of conduction disturbance short of complete heart block.[5] Previous cardiac biopsy specimens have shown characteristic mitochondrial abnormalities[3,5] similar to those seen in skeletal muscle. The morphological hallmark first reported by Luft *et al* is the ragged red fibre, seen with the modified Gomori trichrome stain, which contains peripheral and intermyofibrillary accumulations of abnormal mitochondria.[8] These mitochondrial abnormalities are seen on electron microscopy. The mitochondria are increased in number and may form large aggregates. They may appear morphologically normal but are often abnormally large with vacuoles or dense inclusions (made up largely of lipid). The cristae are disrupted and may form concentric whorls or honeycomb patterns.[6] Excessive accumulation of glycogen particles is also seen. Many of the morphological abnormalities of mitochondria are, however, non-specific and may be seen in other muscle diseases; they probably represent non-specific responses to noxious stimuli.[12]

One other case of cardiac failure in this syndrome has been described.[13] In this case, a 23 year old man, first presented at the age of 12 with high output cardiac failure and again at the age of 16. At the time of his second presentation a profound lactic acidosis and considerable deterioration in the myopathy developed. He responded to treatment with prednisone and thiamine. Endomyocardial biopsy was not performed, and it was suggested that his cardiac failure resulted from a chronic high output state caused by the disturbances in muscle glycolytic metabolism producing excess lactate and pyruvate (akin to beriberi). Our case presented with severe rapidly progressive congestive cardiac failure and it is possible that this was precipitated by other factors. Abnormal cardiac muscle may be more susceptible to the toxic effects of alcohol, and although the drinking history of our patient would not be expected to produce cardiomyopathy in an otherwise normal heart it may have contributed to the speed and severity of his deterioration. In alcoholic cardiomyopathy[14 15] and other cardiomyopathies cardiac muscle may show mitochondrial abnormalities,[16] but the clinical features make our case otherwise typical of mitochondrial myopathy.[7]

We thank Dr Ariela Pomerance for the description of the excised heart and for providing tissue for ultrastructural examination, Mr Rodney Grey for the photograph of the retina, and Dr Hilary Morgan for the neurophysiological studies.

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Addendum

Since this report was prepared, two other cases of Kearns-Sayre syndrome presenting with heart block and heart failure have been reported.[1]

Reference

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Br Heart J 1988;59:491–7

Accessory mitral valve leaflet causing aortic regurgitation and left ventricular outflow tract obstruction

Case report and review of published reports

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SUMMARY Arrhythmias, aortic regurgitation, and symptoms of severe intermittent ventricular outflow obstruction developed in a 14 year old boy with a heart murmur who had been followed from infancy. These were caused by an accessory mitral leaflet, which was successfully removed at open heart operation. A review of 21 previously reported cases found a high incidence of associated cardiac malformations, appreciable subaortic obstruction in most patients, and a consistent attachment of the accessory tissue to the ventricular aspect of the anterior mitral leaflet. The characteristic echocardiographic appearance of a mobile mass arising from the area of aortic-mitral continuity is sufficient for the diagnosis of accessory mitral leaflet and echocardiographic examination will facilitate the surgical management of this condition.

Among the more rare causes of subaortic obstruction are several mitral valve anomalies, including abnormal insertion within the left ventricular outflow tract, prolapse of redundant chordae or a leaflet, and accessory tissue in the subaortic area. Such accessory tissue is uncommon in normally connected hearts. It is a condition singularly amenable to repair without valve replacement. We report a case with several unusual clinical features that illustrates the value of real time echocardiography in diagnosing left ventricular outflow tract obstruction with aortic regurgitation caused by an accessory mitral leaflet.

Case report

A 14 year old boy was admitted to hospital with a two month history of a central stabbing chest pain. He had been seen first at 11 months for an asymptomatic heart murmur that was present at birth, and right heart catheterisation subsequently confirmed the clinical diagnosis of a small ventricular septal defect. Routine outpatient follow up found no change in his physical signs until an early diastolic murmur was heard when he was 14. The patient then recalled several episodes of sharp precordial pain precipitated by strenuous exercise, as well as palpitation and giddy spells unrelated to effort.

The relevant physical findings included an irregularly irregular waterhammer pulse at 80 beats/minute, a systemic blood pressure of 130/70 mm Hg, and an easily palpable thrill along the left sternal border. This corresponded to a harsh systolic ejection murmur radiating widely over the precordium as well as to the patient's neck and back. In addition, there was a grade 2/4 immediate diastolic murmur. The electrocardiogram showed a bizarre pattern of multifocal ventricular extrasystoles, some periods of sinus rhythm with intermittent right bundle branch block, and other periods of junctional rhythm. There was no evidence of ventricular hypertrophy or ischaemia. Chest *x* ray showed a cardiothoracic ratio of 0·53 with pulmonary vasculature. The remainder of the patient's physical examination and laboratory investigations were within normal limits.

Cross sectional echocardiography showed a pedunculated mass originating just beneath the non-coronary cusp. The mass had prolapsed through the aortic valve during systole (fig 1). In addition, there was a large aneurysm of the membranous septum. Pulsed Doppler examination showed moderately

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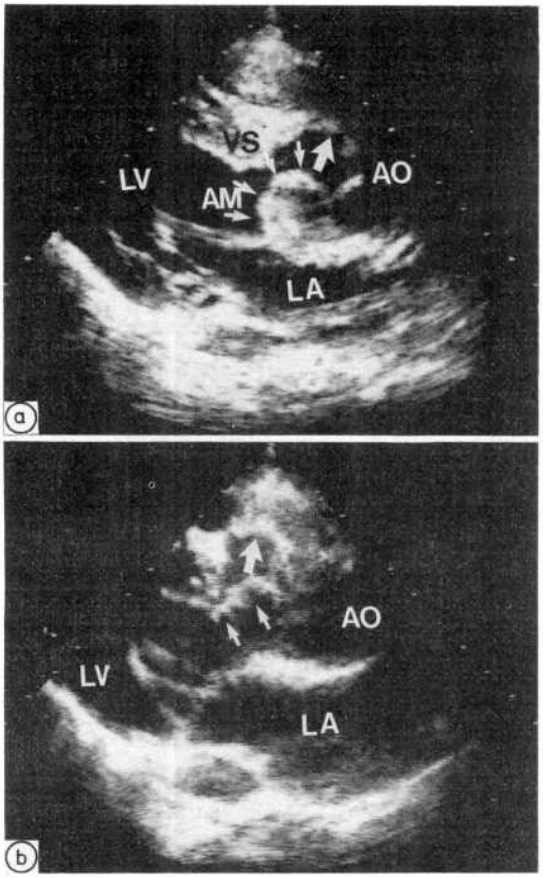

Fig 1 *Cross sectional long axis echocardiograms in systole (a) and diastole (b) showing the prolapse of a large mass of tissue (small arrows) through the aortic valve during ventricular ejection. This tissue fell back against the aneurysm of the membranous septum (large arrow) during diastole. VS, ventricular septum; LV, left ventricle; AO, aorta; LA, left atrium; AM, accessory mitral leaflet.*

severe aortic regurgitation and a velocity of 2·3 metres/second across the left ventricular outflow tract, indicating a gradient of approximately 21 mm Hg. Repeat cardiac catheterisation and angiography confirmed the echocardiographic findings and excluded any intracardiac shunt.

Despite the absence of clinical or laboratory findings to suggest bacterial endocarditis, the echocardiographic appearances were thought to be consistent with a large vegetation and the patient was treated with intravenous antibiotics. Four days after catheterisation his giddy spells recurred, and urgent transaortic exploration of the left ventricular outflow tract was carried out on cardiopulmonary bypass with moderate hypothermia and cardioplegic arrest. The aortic valve was normal, and immediately beneath the commissure between non-coronary and right cusps there was a wide-mouthed aneurysm (20 mm in diameter) of the membranous septum extending into the right ventricle. There was no ventricular septal defect; but, at the lower margin of the aneurysm, a discrete ring of fibrous tissue extended into the outflow tract for about 5 mm and around half its circumference. This did not correspond with the echocardiographic appearances, however, and accordingly a search was made deeper within the left ventricle. This disclosed a mass of soft white tissue attached in several places to the ventricular surface of the anterior mitral leaflet and, on the other side, by well defined chordae, to a small papillary muscle near the ventricular septum (fig 2). This tissue was completely separate from both the subaortic membrane and the aneurysm of the membranous septum (fig 3).

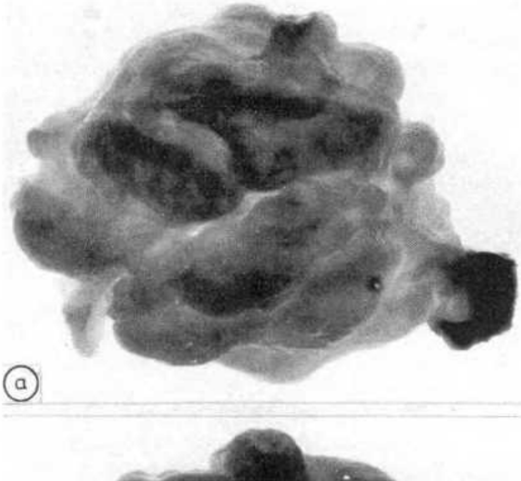

Fig 2 *Transluminated surgical specimen showing the aortic (a) and ventricular (b) sides of the accessory mitral leaflet. The papillary muscle arose near the normal anterolateral papillary muscle and the upper lip was attached to the back of the anterior mitral leaflet in several places. A rudimentary chordal architecture and cusp differentiation is apparent but the leaflet was imperforate.*

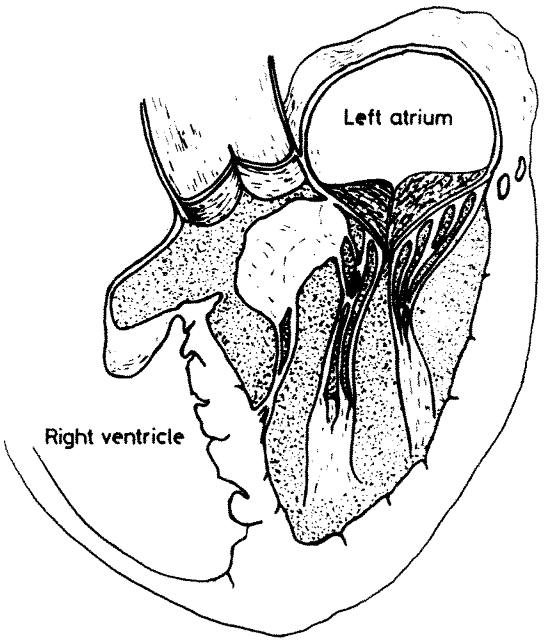

Fig 3 *Diagram of the operative findings showing the relation of the accessory mitral leaflet to the aortic valve and to the aneurysm of the membranous septum.*

The discrete subaortic membrane was enucleated,[1] and the accessory mitral leaflet was excised by sharp dissection. The aneurysm of the membranous septum was plicated on its right ventricular side through the tricuspid valve. Weaning from cardiopulmonary bypass was smooth and uneventful, as was the patient's subsequent postoperative recovery. He was discharged from hospital seven days after operation, when pulsed Doppler echocardiography showed only a trace of aortic regurgitation. The electrocardiogram had returned to normal sinus rhythm.

Discussion

Accessory mitral valve tissue producing subaortic obstruction was first described by MacLean *et al* in 1963[2]; and, in his precise classification, Edwards included this anomaly as a rare cause of subaortic stenosis.[3] During the past decade one or two cases have been reported each year, and it is now possible to characterise this unusual condition in some detail.

The condition usually presents as an asymptomatic heart murmur, although the two youngest patients had low cardiac output from aortic obstruction at three days of age,[4] and congestive heart failure at 14 months.[5] Signs of left ventricular outflow tract obstruction generally develop during the first decade (fig 4) but these have been accompanied by complaints of exercise intolerance, chest pain on exertion, or syncope in less than one third of patients. Usually, the obstruction is severe, with gradients of >50 mm Hg measured by cardiac catheterisation or Doppler echocardiography. There were major associated cardiac defects in 13 of 21 previously described cases[2,5-12] and in our patient, but these did not suggest any particular developmental pattern (table).

Our patient was unusual because he presented with dominant aortic regurgitation and arrhythmias, which, in view of his past history of ventricular septal defect, suggested bacterial endocarditis. It is possible that the aneurysm of the membranous septum provided a bypass around the obstructing accessory mitral tissue until this tissue became sufficiently large to prolapse through the aortic valve. The only other patient to have such a mild gradient across the left ventricular outflow tract also had an aneurysm of the membranous septum.[6] Sudden complete blockage of aortic outflow would account for the patient's chest pain and giddy spells, but the aetiology of his arrrhythmias is less clear. One possibility is that increased left ventricular pressure caused tension on the aneurysm and adjacent conduction tissue, resulting in bundle branch block and the episodes of nodal rhythm. Alternatively, the accessory leaflet itself may have damaged the conduction tissue as it moved within the subaortic area. In either event, the electrocardiogram would be expected to revert to normal, as it did, after operation.

The diagnosis of this and other types of subaortic obstruction has been facilitated greatly by real time echocardiography.[13,14] Although M mode studies showed multiple echoes in the subaortic area,[15] sector scanning clearly differentiates between fixed fibrous tissue and movement of an accessory leaflet into the outflow tract. Whereas a tumour mass or vegetation, theoretically, might produce a similar appearance,

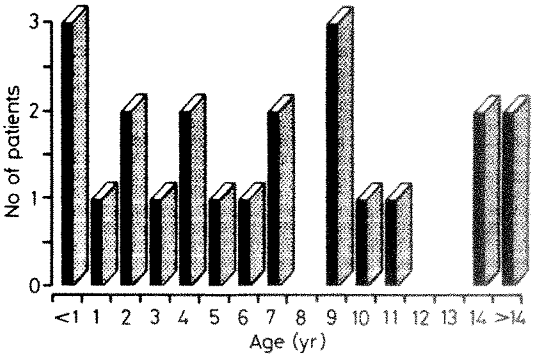

Fig 4 *Age distribution of 22 patients who were found to have a subaortic accessory mitral valve leaflet at operation or necropsy.*

Table *Summary of reported cases of accessory mitral leaflet or tissue in normally connected hearts*

Author	*Age (yr)/ sex of case*	*Presentation*	*Gradient (mm Hg)*	*Surgical approach*	*Accessory tissue*	*Histology*	*Associated lesions*	*Results*
Maclean *et al*[2] (1963)	29/M	Exercise intolerance, murmur since childhood	70	Aortotomy	2 parachute-like structures (5 mm and 15 mm) attached to anterior mitral leaflet		Situs inversus, right SVC	Good
Deal *et al*[9] (1963) Sellars *et al*[10] (1964)	11/F	Seizures; heart murmur, "Known to have subaortic stenosis"	70	Aortotomy	5 balloon-like masses of spherical tissue	Connective tissue similar to normal mitral valve	Membranous subaortic stenosis. Supravalvar mitral ring; bicuspid aortic valve; single sinus origin of coronary	Died POI Accessory tissue not excised
Kelly *et al*[17] (1972)	7/M		130	Ventriculotomy	On anterior mitral leaflet		Dextrocardia, subaortic ring	Good
Cooperberg *et al*[15] (1976)	9/M	Asymptomatic	80	Aortotomy then ventriculotomy	Parachute-shaped, attached to anterior mitral valve ring, chordae attached to septum and papillary muscles			Good
Mathewson *et al*[4] (1976)	3 d/F	Murmur, low cardiac output	62	Aortotomy then ventriculotomy	Pedunculated mass originating from midpoint of junction of mitral annulus and anterior leaflet			Died in operating theatre
Freedom *et al*[12] (1977)	8 mnths/ not known		40	None (Postmortem specimen)	Nodular gelatinous mass of undifferentiated endocardial tissue from aortic leaflet of mitral valve and contiguous membranous septum		Ventricular septal defect, coarctation	Died
Kohda *et al*[18] (1979)	2/F	Heart murmur at 14 months	50	Aortotomy	Accessory tissue attached to anterior mitral leaflet with 3 chordae	Fibrous tissue		Mild mitr regurgitat
Kuribayashi *et al*[20] (1979)	3/M	Heart murmur at 1 month, syncope and chest pain on exertion	100	Aortotomy then left atriotomy	White tissue with chordae attached to anterior leaflet of mitral valve and septum	Fibrous tissue	Dextrocardia	Good
Nanton *et al*[8] (1979)	9/F	Murmur from 1st year	100	Aortotomy	Balloon-like, 2 2 cm × 1 3 cm. Attached in concave arc below left coronary leaflet and to LV wall. Chordae to anterolateral papillary muscle and lateral wall of LV		Discrete subaortic ridge, muscular VSD, accessory tricuspid tissue, 2 coronary ostia in left sinus	Died in lo cardiac output. Accessory tissue not excised
Gomes *et al*[5] (1980)	14 mnths/ M	Murmur from birth, congestive heart failure	90		1 2 cm × 4 cm nodular, flap-like fibrous tissue attached to base of anterior mitral leaflet	Valve-like structure	Partial AV septal defect; left SVC	Mitral insufficien otherwise satisfactor
Tanimoto *et al*[6] (1981)	10 mnths/ F	Heart murmur from birth	26	Aortotomy	Chordae attached to mitral valve ring, aortic annulus, and LV free wall	Fibrous tissue	Supravalvar aortic stenosis; septal aneurysm	Good
Hatem *et al*[11] (1981)	10/F	Asymptomatic heart murmur at 5 weeks	195	Aortotomy	Sheet-like mass under aortic valve with chordae to septum and papillary muscles	Fibromyoid tissue consistent with valve tissue	Bicuspid aortic valve	Residual 1 mm Hg gradient, reoperatec via left atrium; similar ma removed from base mitral leaf

able *Summary of reported cases of accessory mitral leaflet or tissue in normally connected hearts*

thor	*Age (yr)/ sex of case*	*Presentation*	*Gradient (mm Hg)*	*Surgical approach*	*Accessory tissue*	*Histology*	*Associated lesions*	*Results*
ruta *et al*[7] 983)	5/M	Murmur from birth. Tumour-like mass LVOTO on echo	100	Aortotomy then left atriotomy	25 cm × 30 mm accessory leaflet with multiple chordal attachments to anterior mitral leaflet and free wall of LV	Myxoidal dysplasia. Normal endothelium of mitral cusp	Ring of fibrous tissue on atrial side of anterior mitral leaflet	Good
otta *et al*[21] 983)	14/M	Easy fatiguability; heart murmur at 2½ years	50	Aortotomy then left atriotomy	Attached to anterior mitral leaflet and ventricular septum. Chordae connected to mitral valve chordae	Collagen fibre with myxoid stroma and endothelium		Mild aortic regurgitation
n'kovsky and natow[19] (1984)	6/F	Breathless on exertion; temporary heart pains	100	Aortotomy	20 × 15 mm, arising from anterior leaflet of mitral valve	Like a mitral valve		Good
osay *et al*[14]* 985)	9/M	Aortic stenosis and regurgitation	34	Aortotomy	1·5 × 2 cm "membrane"		Situs inversus, mitral regurgitation	Mild aortic regurgitation
inet *et al*[22]* 985)	4/M	Aortic stenosis and regurgitation	112	Aortotomy				Good
	2/M	Aortic stenosis and regurgitation	44	Aortotomy			VSD	Good
lboliras *et al*[16] 985)	15/M	Exertional dizziness and dyspnoea; mass on echo	100		"Hood" of accessory tissue on anterior mitral valve leaflet		Discrete subaortic membrane	Residual 23 mm Hg gradient; accessory tissue not excised
eldrum-Hanna al[23] (1986)	7/F	Asymptomatic murmur	80	Aortotomy	Attached around leftward part of anterior mitral leaflet and on to septum. Short chordae on free edge			Reoperated 2 years later for discrete subaortic stenosis
scuitto *et al*[13] 986)	4/M	Heart murmur, mass on anterior mitral leaflet on echo	100	Aortotomy then left atriotomy	Folds of leaflet-like fibrous tissue attached to base of anterior mitral leaflet; chordae to both papillary muscle	Myxomatous dysplasia; abnormal mitral valve tissue		Trace of aortic regurgitation. Doppler gradient 25 mm Hg

Three cases reported in two papers.
V, atrioventricular; SVC, superior vena cava; VSD, ventricular septal defect; LVOTO, left ventricular outflow tract obstruction; POD, postoperative ay.

such lesions more commonly originate from cardiac muscle or build up directly upon the low pressure side of a heart valve respectively. The degree of subaortic obstruction may be estimated from Doppler echocardiography,[16] which may avoid the need for catheterisation. Indeed, recently operation has been recommended without invasive studies.[14] Angiography can visualise a mass in the subaortic area but adds little to the diagnosis, and cardiac catheterisation probably is required only to investigate associated cardiac malformations.

The indication for operation was severe left ventricular outflow obstruction in eighteen patients and explorations of an intracardiac mass in two. One neonate who had repair of aortic coarctation subsequently died and was found to have accessory mitral valve tissue at necropsy.[12] In another patient the accessory leaflet was discovered during reoperation for residual subaortic obstruction.[17]

All operations were performed on cardiopulmonary bypass, with a variety of approaches to the accessory leaflet. While aortotomy provides good access,[18 19] identification of the accessory tissue may be difficult when it is accompanied by subaortic stenosis or has collapsed into an empty left ventricle.[8] This is because the accessory mitral valve tissue always lies below any discrete fibrous obstruction. When the relation of the accessory leaflet to the mitral valve cannot be clearly seen through the aorta, or when additional malformations are present on the atrial side of the valve,[7] a left atrial approach has been useful.[11 15 20] Although a systemic ventriculotomy also provides good access,[4 17 21] it is likely to compromise cardiac function and is probably unnecessary.

The gross appearances of the subaortic accessory mitral leaflet have been remarkably constant and are not unlike those of accessory mitral valve tissue described in ventriculoarterial discordance with[23 24] or without[25 26] atrioventricular discordance. In all patients the accessory tissue was attached on the ventricular surface of the anterior mitral leaflet and in most it extended to the septal surface or free wall of the left ventricle. Both in relative and real terms, the accessory leaflet tends to be large. In our patient its diameter exceeded 25 mm, compared with an aortic annulus of 20 mm; and in all other operated cases the width was > 15 mm. Occasionally, a second mass of tissue originates from the membranous septum.[8 11]

The extent of differentiation has been variable and may reflect haemodynamic forces applied to the accessory tissue within the left ventricular outflow tract. The most primitive, nodular, gelatinous mass of undifferentiated tissue was found in an eight month old infant[12]; but most leaflets are parachute or sail shaped with a variable number of well defined chordae anchoring the ends to either or both papillary muscles of the mitral valve, to normal chordae, to the left ventricular free wall, or, as seen in our case, to an accessory papillary muscle. The hood-like structure thus produced presents a concave surface towards the left ventricle, so that in ventricular systole this pouch is distended with blood and is carried into the subaortic area. Histological examination of the accessory leaflet has generally shown fibrous tissue with myxoid dysplasia, analogous to dysplastic mitral valve tissue.[7 13 20]

Because the leaflet is accessory tissue, its removal should in no way compromise the function of an otherwise normal mitral valve, and the results of operation usually have been satisfactory. In fifteen patients in whom the mass was removed completely as a primary procedure, there was one death. This was a three day old baby who had a left ventriculotomy after the tissue could not be identified through the aorta.[4] Two patients had mild mitral insufficiency attributed in one to simultaneous repair of a partial atrioventricular septal defect[5 18]; and three patients (including the one reported here) had trivial aortic regurgitation.[13 22] All survivors remained or became symptom free and none has shown signs of recurrent subaortic obstruction. Failure to remove the tissue, however, has been associated with considerable early mortality[8–10] and a high number of reoperations,[15 16] as has partial or incomplete relief of the subaortic obstruction.[11 23] Since the development of real time echocardiography to demonstrate reliably the accessory leaflet before operation, there have been no operative deaths attributed to this lesion.

Little is known about the aetiology and course when an accessory mitral leaflet is present. It has been suggested that anomalies of the mitral valve and fibrous subaortic stenosis both result from abnormal development of endocardial cushion tissue.[27] Yet, considerable evidence supports the view that discrete subartic stenosis is an acquired malformation,[28–30] while the anlaga of an accessory leaflet probably is present at birth, since the murmur is present early in life, even when there are no other cardiac lesions.[2 7] It is likely that the degree of left ventricular outflow obstruction is progressive, because a gradient of 65 mm Hg at five years increased to 196 mm Hg by 10 years in the only patient who underwent serial left heart studies.[11] Whether this results from enlargement of the accessory leaflet or from narrowing of the outflow tract by a discrete membrane is a question that echocardiography may answer in the future; certainly when the leaflet eventually prolapses through the aortic valve it produces symptoms of severe left ventricular outflow tract obstruction and aortic regurgitation, as seen in our patient.

More widespread availability of sector scanning and Doppler echocardiography may lead to the identification of an accessory mitral leaflet before the development of symptoms or important obstruction to left ventricular outflow. While elective, prophylactic removal of the tissue does not seem to be justified, careful excision of the accessory leaflet can be accomplished without morbidity or mortality. Accordingly, accessory tissue probably should be removed during open heart surgery for any associated cardiac defects to avoid residual and, possibly, progressive left ventricular outflow obstruction.[16]

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Familial atrial standstill caused by amyloidosis

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SUMMARY Three of nine siblings were affected by atrial standstill. Clinical, electrophysiological, and histological findings in two of these cases were studied. Electrophysiological studies showed persistent atrial standstill in one and partial atrial standstill in the other. Biopsy specimens of the right atria showed amyloid deposits, but specimens of the right ventricles and skin did not. Neither patient had peripheral neuropathy, gastrointestinal disorder, or renal dysfunction. Familial atrial standstill is usually associated with peripheral neuropathy.

In the two cases studied amyloid deposition mainly affected the atrium, rather than the ventricles or other organs, and caused atrial standstill.

Amyloidosis is a cause of atrial standstill.[1–3] The most common clinical feature of cardiac amyloidosis is rapidly progressive heart failure[4 5]; familial amyloidosis is usually also associated with peripheral neuropathy.[6] We report on three cases of familial atrial standstill caused by amyloidosis in which there were no cardiac symptoms or peripheral neuropathy.

Case reports

CASE 1

A 36 year old man had a sudden onset of left hemiparesis on 29 October 1984. Cerebral infarction was diagnosed and bradycardia and cardiomegaly were found. On 29 November 1984 he was admitted to our hospital for further evaluation. On admission his pulse was regular at 48 beats/min and blood pressure was 140/80 mm Hg. A grade 2/6 ejection systolic murmur was heard along the left sternal border. The second sound was split widely and the width of splitting increased during the inspiratory phase. Neurological examination showed left hemiparesis and a mild speech disturbance.

An electrocardiogram showed a ventricular rate of 39 beats/min with complete right bundle branch block and a QRS width of 0·12 s. No P waves were found in any of the leads. Intravenous atropine sulphate (1·0 mg) and exercise increased the ventricular rate to 64 and 118 beats/min, respectively, but P waves remained absent.

Chest *x* rays showed cardiomegaly with a cardiothoracic ratio of 0·6. The echocardiogram showed dilatation of the right atrium with no A waves on the anterior mitral leaflet, but the wall thickness and contraction of the left ventricle were normal.

Cardiac catheterisation showed no a waves on the right atrial pressure curve. An intracardiac electrogram from the right atrium showed no A waves, fibrillary waves, or any other electrical activity. No extrasystoles could be induced by right atrial stimulation even at an output of 10 V. On the other hand, intrinsic ventricular contractions had a R wave amplitude of 14 mV, and artificial stimulation produced right ventricular activation at 0·3 V.

Biopsy samples from the right atrial wall showed amyloid deposits and considerable muscle loss with replacement fibrosis. But samples from the right ventricle, skin, and rectum showed no evidence of amyloid deposition.

The patient had a permanent pacemaker implanted and has been treated with oral anticoagulants to prevent systemic embolism. He continues to do well with regular visits to our outpatient clinic.

CASE 2

The 34 year old brother of case 1 was found to have bradycardia and cardiomegaly at the age of 27. On 30 November 1983 he was admitted to hospital with lower abdominal pain of sudden onset which was accompanied by an increase in the serum concentrations of glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and lactate dehydrogenase. Lower abdominal pain disappeared in a few days and enzyme concentrations returned to normal within two weeks, but the cause of lower abdominal pain was

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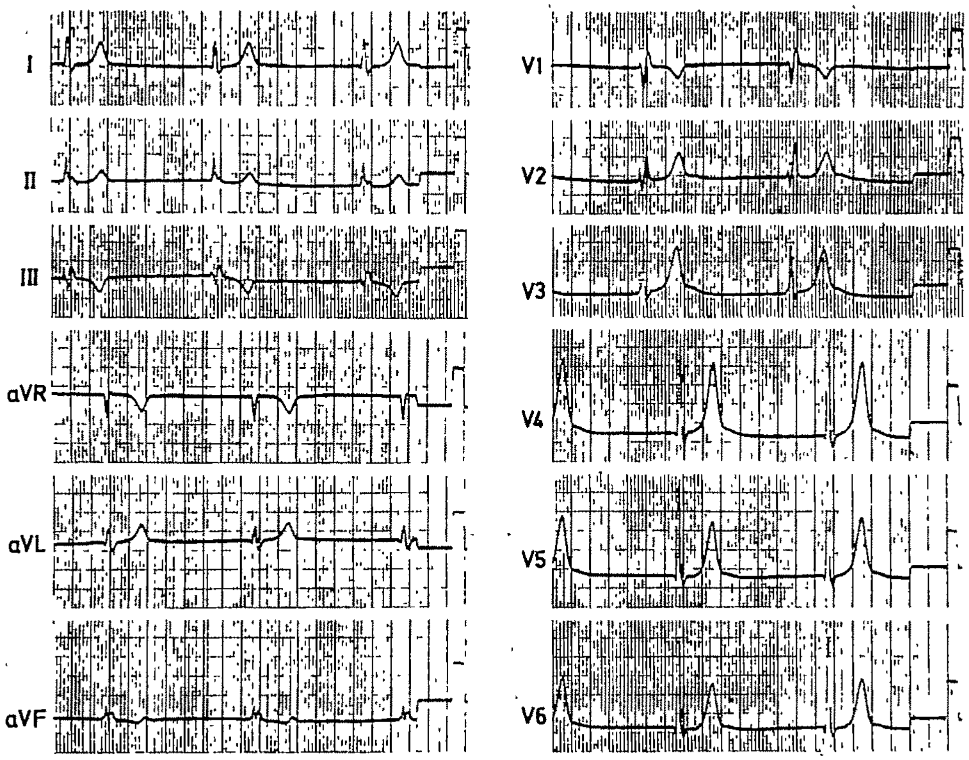

Figure *Electrocardiogram of case 1 showing absence of P waves and slow regular atrioventricular junctional rhythms in all leads.*

never determined. He was admitted to our hospital for further evaluation on 31 March 1984.

On admission his pulse was regular at 35 beats/min and blood pressure was 140/80 mm Hg. There was no peripheral oedema and the liver and spleen were not palpable. A grade 2/6 ejection systolic murmur was heard along the left sternal border. The second sound was widely split and splitting increased during the inspiratory phase. The neurological examination was normal.

An electrocardiogram showed a ventricular rate of 44 beats/min with a QRS width of 0·08 s. No P waves were found in any leads. By contrast, an electrocardiogram obtained seven years earlier showed occasional low voltage P waves (≅0·1 mV) which were conducted to the ventricles, and one recorded a year earlier showed low voltage atrial flutter waves (≅0·05 mV) with a cycle length of 180 ms on leads II, III, and aVF accompanied by a ventricular rate of 40 beats/min. Intravenous atropine sulphate (1·0 mg) and exercise at our clinic increased the ventricular rate to 72 and 120 beats/min respectively, but no P waves appeared. Chest *x* rays showed cardiomegaly with a cardiothoracic ratio of 0·64.

An echocardiogram showed dilatation of the right atrium, no A waves on the anterior mitral leaflet, and normal thickness and contraction of the ventricular wall (as in case 1).

Cardiac catheterisation showed no a waves on the right atrial pressure curve. A right atrial intracardiac electrogram, however, showed very low voltage flutter waves with a cycle length of 175 ms. A simultaneous surface electrocardiogram did not show flutter waves in any leads. Atrial capture could not be achieved with stimuli up to 10 V. On the other hand, the right ventricle showed normal response to stimulation at 0·5 V and R wave amplitude was normal.

Biopsy specimens of the right atrium, right ventricle, and skin were obtained for pathological examination. Only the right atrium contained amyloid deposits (as in case 1). Specimens from the right ventricle and skin were normal.

This patient also had a permanent pacemaker implanted because of considerable bradycardia. He remains well.

CASE 3

The 47 year old brother of the two previous patients was found to have bradycardia and cardiomegaly (cardiothoracic ratio 0·66) at another hospital when he was 37. An electrophysiological study was performed at the time, and a right atrial intracardiac electrogram showed no A waves. The right ventricle responded to stimulation at 0·6 V and R wave amplitude was 5·2 mV. Atrial standstill was diagnosed. A biopsy specimen of the right ventricle showed no abnormalities.

This patient also had a permanent pacemaker implanted for considerable bradycardia at the age of 42. When he was 46 pretibial oedema developed and chest *x* rays showed an increase of cardiothoracic ratio to 0·75. After a one month stay in hospital the pretibial oedema disappeared and his cardiothoracic ratio fell to 0·69. He is being followed at another outpatient clinic and his condition has not deteriorated.

Six other siblings of the above patients (five women and one man) have not been examined.

Discussion

Although familial atrial standstill has been reported,[7–9] its aetiology was confirmed only by Allensworth *et al* and Harrison and Derric. Allensworth *et al* studied three siblings with atrial standstill and showed right atrial amyloid deposits in one of them.[1] Harrison and Derric reported two siblings with almost identical clinical and electrocardiographic features, and showed right atrial amyloid deposition in one.[2] There is also a report by Williams *et al* on familial atrial standstill that reports considerable muscle loss in only the right atrial wall with replacement fibrosis and no evidence of amyloid deposition.[10]

On the other hand, many cases of familial amyloidosis have been reported. In most of them the characteristic clinical findings are associated with peripheral neuropathy,[6 11] but cardiac failure is also found,[12] though less often. There are also many reports of cardiac amyloidosis.[4 5] The most common clinical feature is congestive heart failure, which is often refractory to treatment. Although electrocardiograms in cases of cardiac amyloidosis and familial amyloidosis frequently show sinus node dysfunction, abnormalities of atrioventricular conduction and other arrhythmias,[13 14] atrial standstill is rarely seen.

Familial atrial standstill caused by amyloidosis was diagnosed in our three cases. None of them had peripheral neuropathy, rapidly progressive cardiac failure, gastrointestinal disorder, or renal dysfunction. The clinical, electrophysiological, and pathological findings of our cases differ from those of familial amyloidosis or cardiac amyloidosis reported earlier. Although the cases of Allensworth and Harrison seem to resemble our cases clinically, electrophysiologically, and pathologically, they did not have the same electrophysiological and pathological findings in the ventricle. Frederiksen *et al* stated that in familial amyloidosis, "Case reports show a high degree of uniformity within each family, whereas the symptoms may vary considerably from one family to another."[12] We agree, and we believe that the most important finding in our series was that amyloid deposition mainly affected the atrium rather than the ventricle or other organs and caused atrial standstill.

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Case reports

Triggered activity as a mechanism of recurrent ventricular tachycardia

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SUMMARY Triggered activity was shown to be the likely mechanism of recurrent tachycardia in a 28 year old Vietnamese man. During baseline electrophysiological testing the tachycardia was induced consistently by prolonged atrial or ventricular pacing but not by premature extrastimuli. Moreover, the tachycardia coupling intervals varied directly with the cycle length of the initiating drive. Procainamide and propranolol did not suppress tachycardia, but verapamil terminated it and prevented its reinitiation. The origin of the tachycardia was localised to the left ventricular inferoapical segment and four direct current countershocks of 200 J each delivered via an electrode catheter abolished the tachycardia. During 12 months of follow up the patient was not treated with antiarrhythmic agents and the tachycardia did not recur.

Triggered activity resulting from delayed afterdepolarisations has been demonstrated in isolated human or canine cardiac tissue under conditions of digitalis toxicity,[1 2] catecholamine superfusion,[3 4] and acute myocardial infarction.[5] In these preparations, pacing can induce sustained rhythmic activity that results from repetitive triggered activity in which the mechanism is not reentry. Although sporadic case reports have attempted to implicate triggered activity as a mechanism of cardiac arrhythmias in man,[6-10] convincing proof that it causes arrhythmias is still lacking.

We report a young patient in whom recurrent ventricular tachycardia was probably caused by triggered activity and was successfully controlled by ablation with an electrode catheter.

Case report

A 28 year old Vietnamese man with chronic schizophrenia was admitted to our medical centre in September 1986 because he had had recurrent palpitation since the age of 24. Palpitation occurred one to three times a month and was associated with dizziness, vomiting, and presyncope. Repeated electrocardiograms during palpitation showed a wide complex tachycardia at a rate of 180—200 beats/minute with a QRS configuration of right bundle branch block and a frontal plane axis of −45°. The patient was not taking cardiac or psychotropic medications. An electrophysiological study in 1983 showed that the tachycardia was ventricular in origin. Propranolol, lignocaine, and procainamide did not prevent the induction of ventricular tachycardia, but intravenous verapamil suppressed it. Despite maintenance treatment with high dose verapamil (480 mg/day) and then with diltiazem (360 mg/day) the patient had several recurrences of symptomatic ventricular tachycardia over the next two years and required frequent admissions to hospital. Therefore, he was admitted electively so that he could be assessed for ablation of ventricular tachycardia by percutaneous electrode catheter. The patient was a well developed young man with a heart rate of 70 beats/minute and systemic arterial blood pressure of 110/70 mm Hg. Physical examination was normal. The baseline electrocardiogram was normal except for minor T-wave inversion in leads

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III and aVF. An M mode and cross sectional echocardiogram, radionuclide angiography, and a right heart catheterisation showed no abnormality.

ELECTROPHYSIOLOGICAL STUDY

After he gave his informed consent, an electrophysiological study was performed while he was fasting and unsedated. Four quadripolar electrode catheters were positioned at the high lateral right atrium, His bundle region, coronary sinus, and right ventricle. Surface leads V1, I, and aVF and the intracardiac electrograms were displayed on a VR-12 oscilloscope (Electronic for Medicine) and recorded at a paper speed of 100 mm/s. Programmed stimulation was performed with a programmable stimulator (Bloom and Associates) with pulse duration of 2 ms and a current strength of twice diastolic threshold.

The coupling interval for ventricular tachycardia was defined as an interval from the earliest ventricular activation of the last paced QRS complex to that of the first beat of induced ventricular tachycardia. The relation between ventricular tachycardia coupling intervals and the initiating drive length was analysed by linear regression.

Results

The baseline atrio-His (AH) interval was 90 ms and the His-ventricle (HV) interval was 40 ms. There was no evidence of dual atrioventricular nodal pathways or nodoventricular accessory pathways. Programmed stimulation induced a sustained ventricular tachycardia that had the same configuration as the clinical ventricular tachycardia. The diagnosis of ventricular tachycardia was confirmed by the presence of fusion beats and complete atrioventricular dissociation, and by the absence of a His deflection preceding the QRS complexes.

INDUCTION AND TERMINATION CHARACTERISTICS

The ventricular tachycardia was induced consistently after or during 10–20 seconds of atrial pacing at cycle lengths ranging from 400 to 340 ms (fig 1). Pacing at shorter cycle lengths resulted in atrioventricular nodal Wenckebach block and failed to induce ventricular tachycardia. After administration of intravenous atropine 0·4 mg, atrioventricular nodal Wenckebach cycle length decreased from 330 to 270 ms, and ventricular tachycardia could now be induced by atrial pacing at cycle lengths of 330–270 ms (fig 1). Induction of ventricular tachycardia was never preceded by the development of fascicular or right bundle branch block, which makes the involvement of bundle branches in the tachycardia circuit unlikely. Incremental right ventricular pacing (pre-atropine) at cycle lengths from 350 to 220 ms also consistently induced clinical ventricular tachycardia. In contrast, atrial extrastimuli never initiated ventricular tachycardia. A single ventricular extrastimulus induced ventricular tachycardia on only two occasions with a V_1V_2 of 320 ms and 280 ms, respectively and ventricular tachycardia was never induced with two or three double ventricular extrastimuli.

The coupling intervals of induced ventricular tachycardia seemed to vary directly with the initiating paced cycle lengths. As the atrial drive length decreased from 400 to 270 ms, the coupling intervals shortened from 330 ms to 235 ms. A similar shortening was seen during ventricular overdrive pacing but did not reach statistical significance (fig 2). The cycle length of induced ventricular tachycardia ranged from 270 to 310 ms and seemed to depend upon the initiating drive length. A precise determination of this relation, however, could not be obtained because of spontaneous variations of 10 to 30 ms in the cycle length of induced ventricular tachycardia. The average cycle length of ventricular tachycardia was 310 ms at initiating (atrial or ventricular) drive lengths of 300 to 400 ms, 290 ms at drive lengths of 260 to 290 ms, and 270 ms at drive lengths of 250 ms or less (fig 1).

Right ventricular overdrive pacing (cycle lengths 260 to 220 ms) consistently terminated ventricular tachycardia but single and double ventricular extrastimuli failed to terminate or reset the ventricular tachycardia. Rapid atrial pacing had no effect on the tachycardia. Ventricular tachycardia was never entrained during atrial or ventricular pacing.

After isoproterenol infusion (2 μg/min) the sinus cycle length decreased from 560 to 340 ms and there was a spontaneous induction of clinical ventricular tachycardia with a cycle length of 250 ms. The ventricular tachycardia could not be terminated by overdrive pacing and the termination required discontinuation of isoproterenol and administration of 10 mg of intravenous verapamil. After verapamil sustained ventricular tachycardia could still be induced, but its cycle length had lengthened from 250 ms to 420 ms. The ventricular tachycardia could no longer be induced after infusion of an additional 10 mg of intravenous verapamil.

TACHYCARDIA MAPPING AND ABLATION

Electrode catheter mapping[11] during induced ventricular tachycardia localised the site of earliest endocardial activation to the left ventricular inferoapical region. At this site endocardial activation occurred 20 ms before the onset of ventricular activation on the surface electrocardiographic leads. Fragmented electric potentials were not noted at any

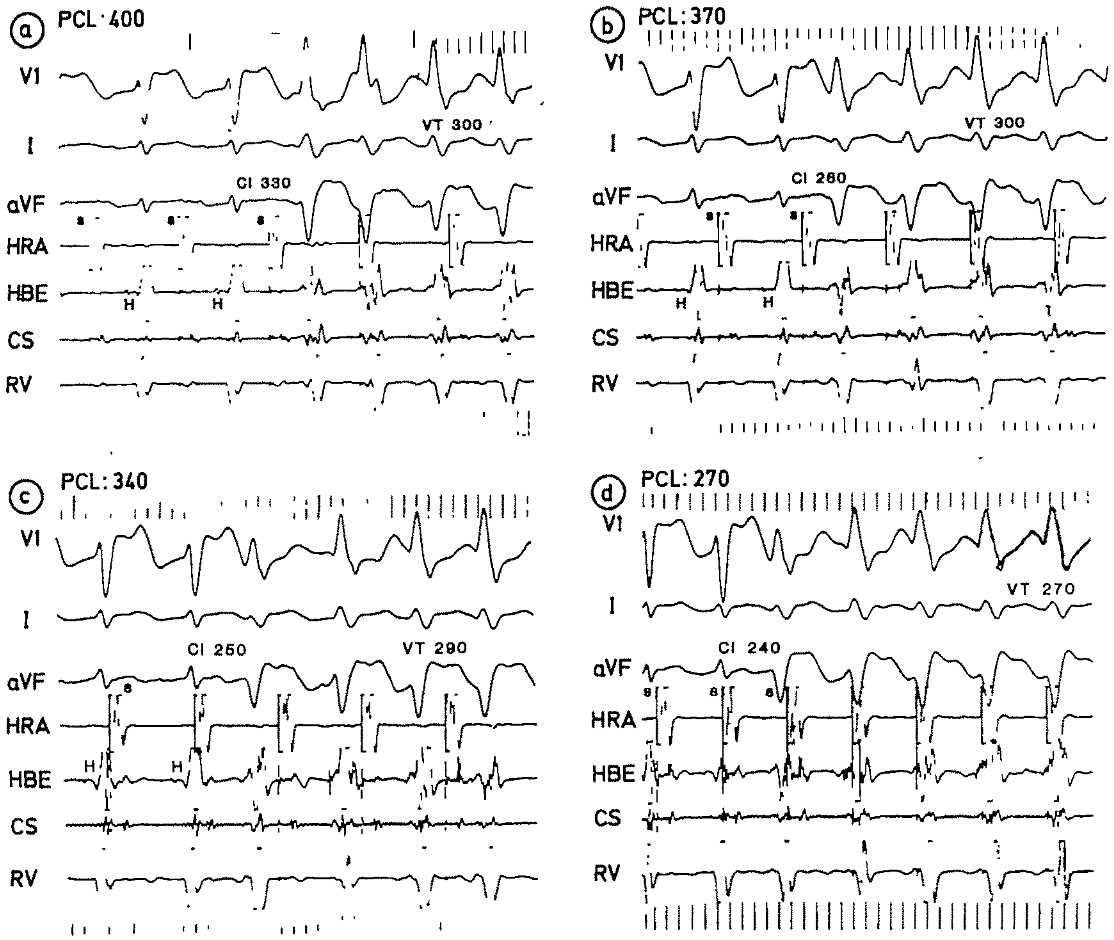

Fig 1 *Atrial induction of ventricular tachycardia (VT). VT was induced during atrial pacing at cycle lengths of 400, 370, 340, and 270 ms (a–d). During induced VT the QRS complexes were not preceded by His deflection, and there was complete atrioventricular dissociation. Note that the VT coupling intervals (CI) vary directly with the atrial paced cycle length (PCL). The CI was 330 ms at PCL of 400 ms (a), 260 ms at PCL of 370 ms (b), 250 ms at PCL of 340 ms (c), and 240 ms at PCL of 270 ms (d). The recordings also show the dependency of VT cycle length on the initiating drive length. The VT cycle length was 300 ms at PCL of 370 ms (b), 290 ms at PCL of 340 ms (c), and 270 ms at PCL of 270 ms (d). Recordings include surface leads V1, I, and aVF and bipolar electrograms from the high right atrium (HRA), the region of the His bundle (HBE), the coronary sinus (CS), and right ventricle (RV). Heavy time lines represent 1 s. S, atrial stimulus; H, His bundle deflection.*

site in the ventricles. Catheter ablation of the ventricular tachycardia was achieved under thiopentone sodium (pentothal) anaesthesia with four direct current countershocks of 200 J each at the site of the earliest endocardial activation. The distal catheter pole acted as a cathode and the posterior electrode pad (R–2 industries) as an anode. This did not suppress the inducibility of ventricular tachycardia but the cycle length of induced ventricular tachycardia lengthened from 310 to 420 ms.

After ablation creatine kinase peaked at 1515 U/l with a 14% MB isoenzyme fraction. The electrocardiogram showed 3–5 mm ST-segment elevation in leads II, III, and aVF, and a cross sectional echocardiogram showed moderate hypokinesia of the left ventricular inferior wall; both abnormalities resolved three days later. Subsequently, he had an uncomplicated hospital course. One week later, repeat electrophysiological testing was performed, during which ventricular tachycardia could no longer be

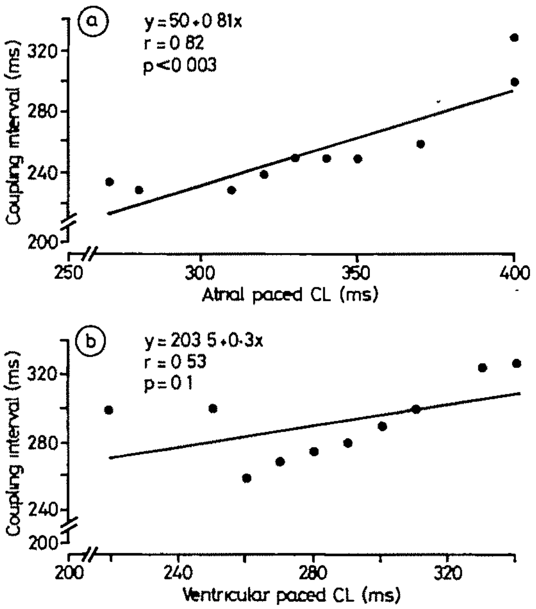

Fig 2 *Relation of paced cycle lengths with the coupling intervals of ventricular tachycardia induced during atrial (a) and ventricular (b) overdrive pacing. See text for explanation.*

induced either before or after administration of isoproterenol (1 to 4 μg/minute), despite the use of incremental pacing and three extrastimuli at two right ventricular sites.

The patient was discharged home without antiarrhythmic treatment, and he has not had palpitation during a follow up of 12 months.

Discussion

MECHANISM OF VENTRICULAR TACHYCARDIA

Tachycardias reproducibly initiated and terminated by programmed stimulation may be caused by reentry or triggered activity. Several findings suggest that triggered activity was the mechanism of ventricular tachycardia in our patient. First, the ventricular tachycardia was induced consistently by atrial and ventricular incremental pacing, but not by premature stimuli. Second, the ventricular tachycardia coupling intervals varied directly with the cycle length of the initiating paced drives. Third, the ventricular tachycardia showed considerable sensitivity to the effects of catecholamines: ventricular tachycardia became easier to induce, faster in rate, and more difficult to terminate after administration of isoproterenol. Fourth, the rate of ventricular tachycardia seemed to depend upon the cycle length of the initiating drive. This relation was seen for ventricular tachycardia induced by both atrial and ventricular pacing. Finally, the ventricular tachycardia was successfully terminated and suppressed by verapamil, whereas procainamide and propranolol were ineffective.

These findings are atypical of reentry and when taken together are best explained by triggered activity.[2-4] Under experimental conditions, sustained tachycardias caused by triggered activity have been shown to be induced more readily by prolonged incremental pacing than by extrastimuli.[3,4] Triggered activity was induced by prolonged overdrive pacing in 83% of ouabain perfused isolated canine Purkinje fibres, in 39% of fibres by a single extrastimulus, and in 48% of fibres by double extrastimuli.[3] Unlike reentrant arrhythmias in which the ventricular tachycardia coupling intervals are inversely related to the initiating drive length,[12] the coupling intervals of triggered tachycardias have been demonstrated to vary directly with the cycle length of the initiating drive.[3,4] This relation may be more complex when triggered arrhythmias are induced by short drive lengths. Under these conditions, the coupling intervals may shorten or lengthen, depending on whether the first or second delayed afterdepolarisation attains threshold and initiates sustained tachycardia.[2] The responsiveness of ventricular tachycardia to verapamil also accords with the ionic mechanism of triggered activity, which is thought to be mediated by an enhanced inward slow channel current carried by calcium.[13] None the less, none of the above criteria is specific enough reliably to differentiate triggered rhythm from other mechanisms and, therefore, a reentrant mechanism, although unlikely, cannot be excluded in our patient.

Previous data on triggered activity causing clinical arrhythmias are scarce. Zipes *et al* reported three patients in whom atrial pacing consistently induced ventricular tachycardia; triggered activity was the suspected mechanism in one patient.[6] Belhassen *et al* suspected triggered activity in a patient with recurrent sustained ventricular tachycardia in whom verapamil terminated ventricular tachycardia and prevented its reinitiation.[7] Similarly, Lin *et al* reported four patients[8] and Ward *et al* five patients[9] with recurrent ventricular tachycardia in whom ventricular tachycardia was induced by overdrive pacing, extrastimuli, or both, and was terminated or slowed by calcium antagonists. Like our patient, these patients had no identifiable heart disease, and the QRS complexes during ventricular tachycardia had a right bundle branch block configuration and left axis. In most of these patients, the tachycardia characteristics seemed to be those of reentry rather than the triggering. In no patient did the ventricular tachycardia coupling intervals progressively decrease or the ventricular tachycardia rate increase as the initiating drive length was shortened. The patient reported by us is the first who met the proposed electrophysiological criteria for triggered activity.[14] There is also controversy on whether this form of verapamil-sensitive ventricular tachycardia originates in the region of left posterior fascicle or in the ventricular myocardium. In the five patients reported by Ward *et al*, the HV intervals ranged from + 15 to − 20 ms, and they suggest a fascicular origin for the tachycardia.[9] In our patient, the ventricular tachycardia was probably myocardial in origin because His deflections could not be recorded during ventricular tachycardia, and the mapping studies localised the tachycardia in the inferoapical segment of the left ventricle.

Percutaneous catheter ablation has been reported to be an effective treatment in patients with drug resistant ventricular tachycardia, which has a reentrant mechanism.[15 16] The case we report shows that sustained ventricular tachycardia caused by a triggered mechanism may also be responsive to this technique. For reasons that are unclear, the ventricular tachycardia could be induced immediately after delivery of four direct current counter shocks, but could no longer be induced during repeat electrophysiological testing one week later. Moreover, the patient has stayed free of recurrent palpitation during a follow up of 12 months. It could be that healing at the site of catheter ablation in the first week led to a late resolution of the inducibility of ventricular tachycardia. This, however, could not be confirmed.

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Acute myocardial infarction after a wasp sting

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SUMMARY A 56 year old man with ischaemic heart disease and known allergy to wasp venom was stung in the mouth by a wasp and within four hours sustained an acute myocardial infarction. This complication has been described on only three previous occasions. Possible pathogenic mechanisms include the anaphylactic reaction itself, the action of wasp venom constituents, and therapeutic intervention with adrenaline.

Anaphylaxis after an insect sting usually presents as hypotension, bronchospasm, and laryngeal oedema. Electrocardiographic changes,[1-3] chest pain,[4] and three instances of acute myocardial infarction[5]—two in North America and one in Sweden—have been described. We report a case of myocardial infarction complicating a wasp sting in the United Kingdom.

Case report

A 56 year old man was stung in the mouth by a wasp in a glass of lager. Within two minutes he became acutely breathless and experienced tight central chest discomfort. He had a history of urticaria after a previous wasp sting. Three years before he had had an uncomplicated inferior myocardial infarction but a subsequent exercise electrocardiogram had suggested multivessel disease. Two years later he had undergone three vessel coronary artery bypass grafting although he was symptom free at this time. He had remained symptom free after operation and had a good exercise tolerance.

When he arrived at an accident and emergency department 40 minutes after being stung he was restless and hypotensive (systolic blood pressure 65 mm Hg). Periorbital oedema was evident. An electrocardiogram (figure a) showed abnormal Q waves in leads II, III, and aVF, which had been recorded on earlier electrocardiograms and were consistent with the previous inferior myocardial infarction. There was early acute ST-segment elevation both in these leads and in the chest leads V2–V5. Treatment for anaphylactic shock was started with hydrocortisone, chlorpheniramine, and subcutaneous adrenaline; he improved. The electrocardiographic changes were not recognised and he was discharged home. He experienced no further chest pain but was referred for further assessment 10 days later with fatigue, breathlessness, and weight gain. On examination the blood pressure was 95/60 mm Hg with a heart rate of 82 beats/min. The venous pressure was raised with an 8 cm V wave and a distinct third heart sound was heard. An accelerated iodiojunctional rhythm with right bundle branch block and changes typical of a substantial transmural anterior myocardial infarction were recorded. He subsequently reverted to sinus rhythm but abnormal Q waves persisted in leads V2—V5 (figure b) and the T waves in II and aVF (that had previously been upright) remained inverted. A multiple gated acquisition study showed a dilated left ventricle, an immobile interventricular septum, and a left ventricular ejection fraction of 0·22 (normal ⩾0·60). Cardiac catheterisation showed poor left ventricular function and thrombosis of all three grafts with occlusion of the left anterior descending artery. Before operation this vessel had been severely narrowed proximally. Anterior and inferior myocardial infarction was confirmed by exercise thallium myocardial scintigraphy.

Discussion

The patient's symptoms immediately after the wasp sting are attributable either to anaphylaxis or to acute myocardial ischaemia or to both. Subsequent events, however, confirmed that he had an acute anterior myocardial infarction, with possible extension of a previous inferior infarction, at or around the time of the wasp sting, and it is tempting to suggest a cause and effect relation. Subsequent coronary angiography suggested that the infarction was caused by

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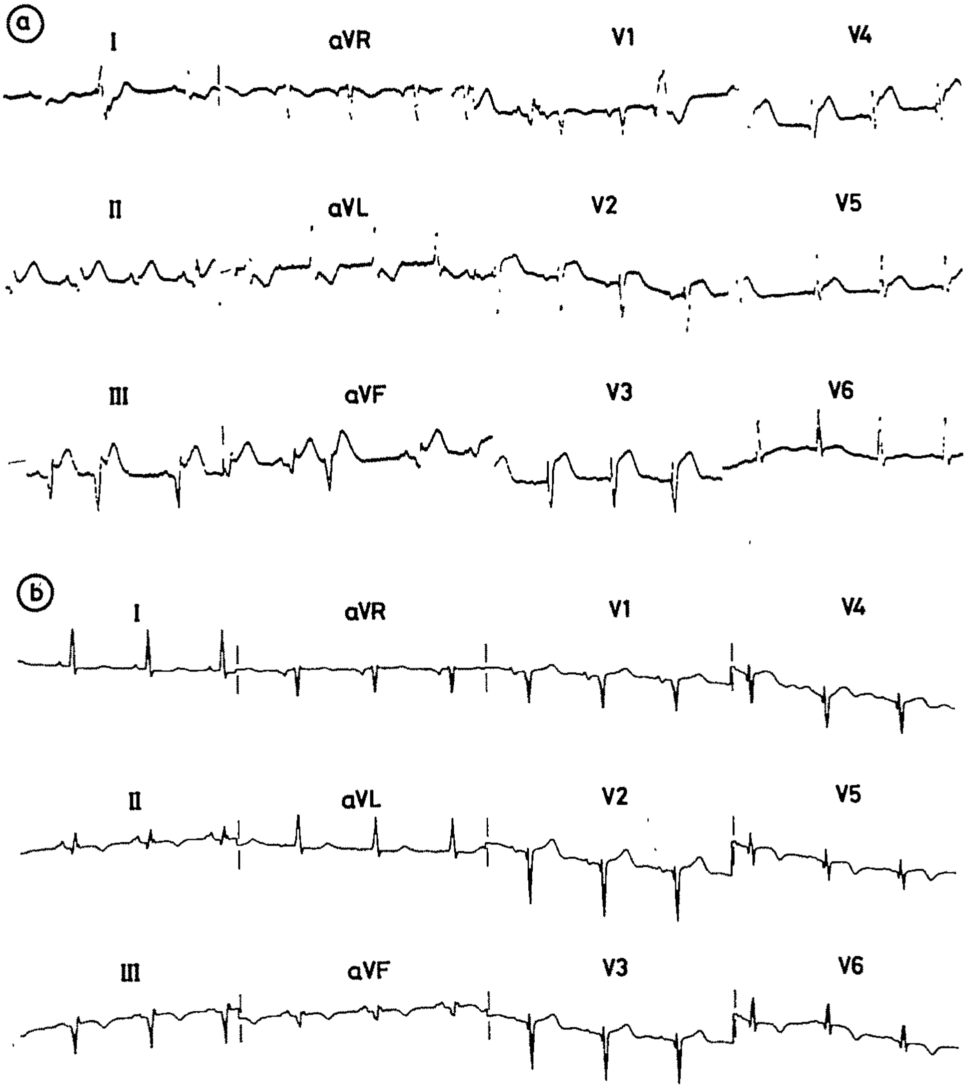

Figure. *Electrocardiogram of patient four hours after wasp sting, showing widespread inferior and anteroseptal ST-segment elevation (a). Resolution had occurred 11 days later (b) but the appearance of abnormal Q/QS waves suggested that a transmural anterior myocardial infarction had occurred.*

occlusion of the left anterior descending artery or the graft to this vessel or possibly both. Without a postoperative angiogram it is impossible to know when graft occlusion occurred. If one or more grafts were already partially occluded, the haemodynamic events at the time of the wasp sting might have sufficiently reduced coronary blood flow to facilitate thrombosis, but other pathogenetic mechanisms are likely to have been operating.

The reaction to a wasp sting can be prolonged or severe in allergic individuals and in some cases anaphylaxis may ensue, with urticaria, circulatory collapse, and bronchospasm. This is the result of a sequence of events including the release of serotonin and histamine and the formation of leukotrienes,[6] some of which are potent coronary vasoconstrictors in various animal species.[7 8] Many pharmacologically active constituents of wasp venom have been isolated including histamine, serotonin, dopamine, noradrenaline, and a bradykinin-like substance which may itself induce histamine release.[9] Endogenous secretion of adrenaline and noradrenaline is stimulated by histamine and serotonin. All these substances can provoke myocardial ischaemia either via profound hypotension or by increasing myocardial oxygen demand through direct inotropic or chronotropic effects in the presence of a compromised myocardial blood supply.

Platelet aggregation is induced by serotonin[10] and adrenaline.[11 12] Adrenaline also accelerates thrombus formation in animals and in man, possibly by increased factor V activity,[13 14] and has been shown in animals to release a thromboplastin-like substance from the walls of blood vessels.[15] It causes both coronary vasodilatation and increased myocardial oxygen demand by direct inotropic and chronotropic effect. It has been used historically as a provocation test for angina pectoris and is often used in the treatment of anaphylactic shock. In two previously reported cases of acute myocardial infarction after wasp stings, chest pain occurred after the administration of adrenaline and diagnostic electrocardiograms were subsequently obtained.[5] In our patient chest pain occurred within minutes of the sting but before adrenaline was given. But the possibility remains that the myocardial infarction was precipitated by exogenous adrenaline, and it is conceivable that the sting and the infarction were not related.

Acute myocardial infarction after an insect sting is rare, only three unequivocal cases have been reported world wide.[5] Since numerous electrocardiographic changes have been reported in association with anaphylaxis and after insect stings in subjects without evidence of coronary artery disease,[1-3] the electrocardiogram at presentation is unlikely to be helpful in predicting which patients are at risk of myocardial ischaemia. It would thus seem reasonable to use adrenaline with caution in those with a history that is suggestive of coronary insufficiency, although adrenaline should not be withheld in this life threatening situation.

We thank Dr Michael Webb-Peploe of St Thomas's Hospital for performing the angiography.

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Coronary artery aneurysms and myocardial infarction: adult sequelae of Kawasaki disease?

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SUMMARY Coronary artery aneurysms developed in a 43 year old man who had suffered an acute myocardial infarction at the age of 30. In childhood he had had an illness that was consistent with Kawasaki disease, and it is suggested that the proximal discrete aneurysms and myocardial infarction may be the adult sequelae of this.

The arteriographic appearance of a coronary artery aneurysm is of localised dilatation of the vessel between two segments that are of normal calibre. Coronary artery aneurysms are not uncommon: they were found in 1·4% of necropsies performed in patients over the age of 16 years.[1] They are usually arteriosclerotic in origin,[2] but may be congenital, occur after injury, dissection, or infection, or be caused by polyarteritis nodosa. Mycotic and syphilitic coronary aneurysms are well described but more recently an additional possibly infective source has been recognised. Kawasaki disease was first described in 1967 in South West Japan as an acute febrile mucocutaneous syndrome with lymphoid involvement and desquamation of the fingers and toes in infants and young children.[3] Coronary artery involvement is a prominent feature of Kawasaki disease and an important cause of death.[4 5] The underlying pathological finding is an arteritis; and coronary aneurysms, ectasia, stenosis, and occlusion are all well recognised sequelae.[5 6]

Case report

A 43 year old male ambulance driver was referred for investigation of atypical chest pain. At the age of eight he had suffered a systemic, febrile illness with generalised lymphadenopathy, a mucocutaneous eruption, and alopecia. He had been in hospital for two months but no further details of this illness were available and no clear diagnosis was made.

He remained well until 1974 when, at the age of 30, he was admitted to hospital with an acute anteroseptal myocardial infarction confirmed on serial electrocardiograms and by cardiac enzyme activity. He made an uncomplicated recovery, and subsequent concentrations of fasting serum lipids were normal.

He remained well until 1986, when he was referred to the Brompton Hospital for investigation of atypical chest pain. He had been adopted and could give no family history, had never smoked, and had no history of venereal disease. He was normotensive and there were no abnormal physical signs.

An electrocardiogram was consistent with an old anteroseptal myocardial infarction. He completed 12 minutes of the standard Bruce protocol with a normal pulse rate and blood pressure response and no changes suggestive of myocardial ischaemia. A chest *x* ray and routine haematological, biochemical, and serological profiles were entirely normal. Cross sectional echocardiography showed two circular echodense areas approximately 1 cm in diameter in the region of the proximal left and right coronary arteries.

Cardiac catheterisation was performed and fluoroscopic screening demonstrated a circular thin rim of calcification just distal to the tip of the coronary catheter when this was engaged in the left coronary ostium (fig 1). Selective coronary arteriography in different projections further defined this lesion and showed that it was closely associated with the proximal left anterior descending artery and moved with it during the cardiac cycle. The left anterior

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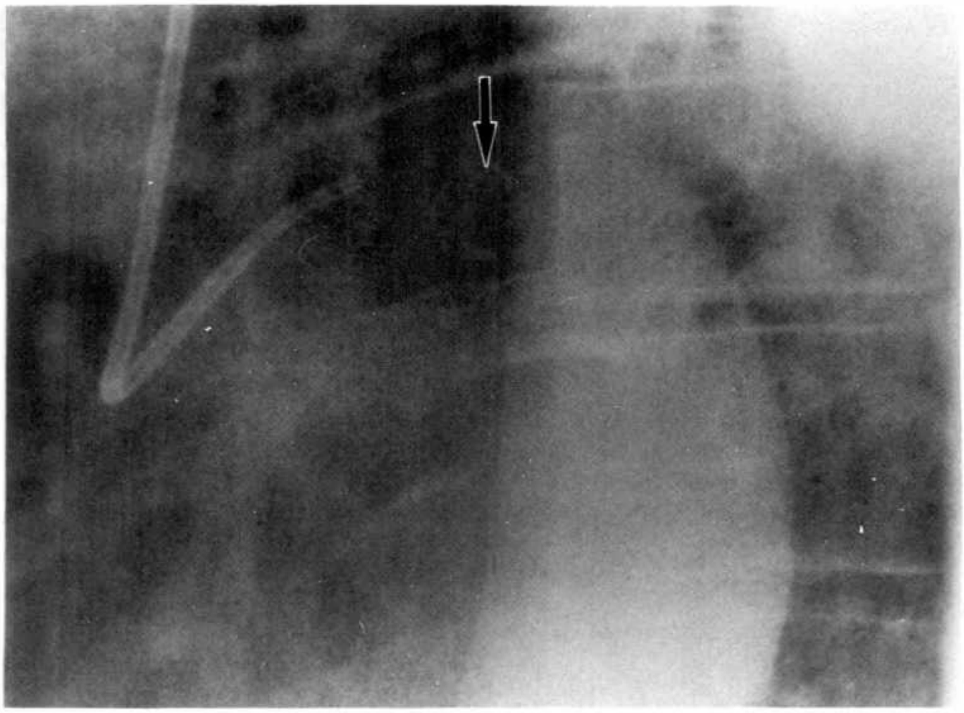

Fig 1 *X ray in the left anterior oblique projection showing brachial coronary catheter engaging the left main stem coronary artery. There is a circular ring of calcification (arrowed), just distal to the tip of the catheter.*

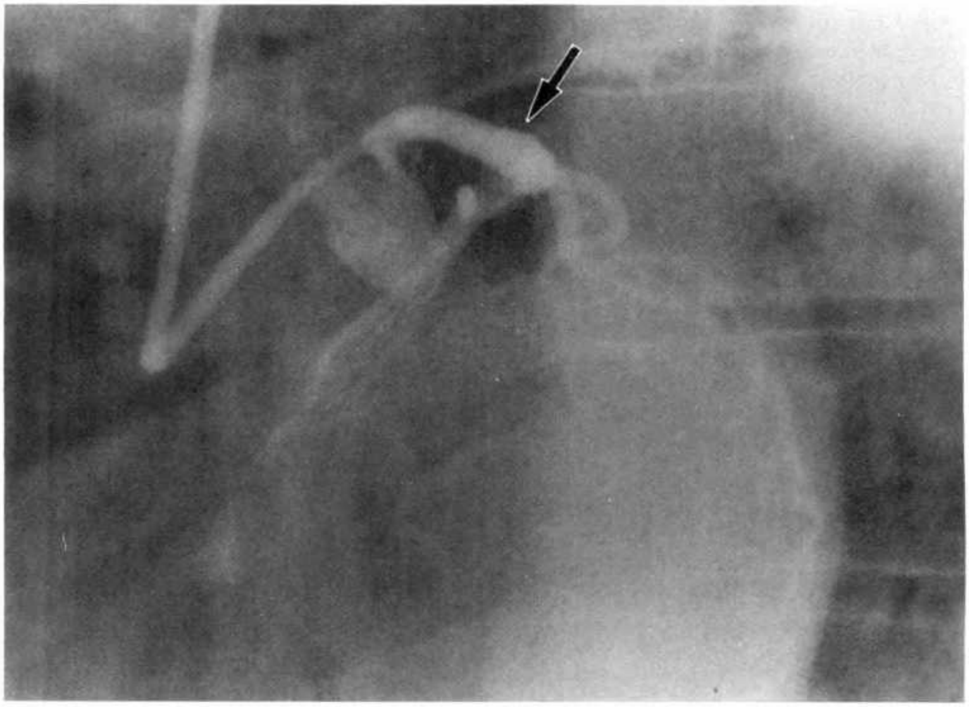

Fig 2 *Selective contrast injection of the left coronary artery via a brachial catheter in the left anterior oblique projection. Contrast is seen to run through the circular ring of calcification (arrowed).*

oblique view (fig 2) was selected because it demonstrated the calcification most clearly, although in this view it seemed to overlie the left main stem. There was a slight irregularity of the left anterior descending artery at the same site, but otherwise the left coronary artery was normal. There was a similar fine, eggshell rim of calcification around the proximal right coronary artery that was clearly seen on fluoroscopy but was difficult to reproduce photographically. This lesion was also attached to the artery, which was itself mildly irregular at the same site. Apart from some slight distal ectasia the remaining right coronary artery was normal. Left ventricular wall movement was normal on cineangiography, with no evidence of previous infarction.

No specific treatment was started because the patient's symptoms had largely resolved; at follow up after six months he remained symptom free.

Discussion

The aetiology of this patient's coronary aneurysms cannot be determined with certainty, but there was strong circumstantial evidence of a childhood illness suggestive of Kawasaki disease. This is supported by the unusual appearance of the aneurysms which are not typical of those occurring in atherosclerosis. The irregularly narrowed lumen together with the surrounding eggshell rim of calcification resembles lesions found in Kawasaki disease.[6] In addition, this patient had no risk factors for atherosclerosis, and there was no evidence for trauma, dissection, polyarteritis nodosa, syphilis, or congenital abnormalities being the underlying aetiology.

We suggest that the likely sequence of events in this patient was that coronary aneurysms formed after Kawasaki disease in childhood and that subsequent thrombus formation may have occurred within the sac of the left anterior descending artery aneurysm. Subsequent temporary occlusion of the artery at this point, or distal embolisation from the thrombus, could have caused the myocardial infarction.

Although it was first reported in 1967, Kawasaki disease is thought to have occurred endemically before then and is now known to occur both endemically and epidemically in children of all races in Asia, North America, and Europe.[7 8] The coronary arteries are affected in 15–25% of cases, resulting in the development of aneurysmal or ectatic segments. Coronary insufficiency and myocardial infarction are known to occur after Kawasaki disease.[9 10]

The prevalence of Kawasaki disease is increasing, with over 67 000 cases reported in Japan. A nationwide epidemic was observed in Japan in April 1979, a second in 1982, and the third was reported during the winter of 1985–6.[11] The epidemiological patterns of the disease suggest an infectious aetiology by an unknown agent, possibly a retrovirus.[12]

Many types of treatment have been used in Kawasaki disease but none is entirely effective. A standard treatment for the associated arteritis has been aspirin. Newburger *et al*[13] concluded from a multicentre randomised trial that high dose intravenous γ globulin is effective in reducing the incidence of coronary artery abnormalities if given early in the course of the illness.

We believe that our patient had Kawasaki disease as a child and that his early myocardial infarction and coronary aneurysms are a consequence of this. Similar cases have been reported,[14] but never with strong circumstantial evidence of the childhood illness, or such unusual angiographic appearances. If the prevalence of the condition rises in the United Kingdom, as has happened in the United States and Japan, then such sequelae may become more familiar.

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Dehiscence of an atheromatous plaque at an aortic valve commissure: an unusual cause of acute aortic regurgitation

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SUMMARY A 78 year old man underwent aortic valve replacement because of acute aortic regurgitation and intractable heart failure. At operation the intact commissure between the left and right coronary cusps of a grossly normal aortic valve was found to have separated from the aortic wall. Histopathological examination of the surgical specimen showed that the site of separation was an atheromatous plaque. This is believed to be the first report of this feature.

Severe aortic regurgitation of acute onset is usually caused by aortic dissections or infective endocarditis. Rarely, blunt chest injury and straining can lead to avulsion of a "normal" aortic valve resulting in acute aortic valve incompetence.[1-3] We describe an unusual cause of acute aortic regurgitation precipitated by dehiscence of an atheromatous plaque at one of the commissures of a previously normal aortic valve. We believe that this feature has not been reported before.

Case report

During a routine visit to his family doctor, a 78 year old man with mild diabetes mellitus was found to have a cardiac murmur suggestive of aortic regurgitation. The murmur had not been noted by his family physician before. There was no history of chest injury or straining. Three weeks later exertional dyspnoea developed and he was admitted to a general hospital. Severe aortic regurgitation and pulmonary oedema were diagnosed. He was managed with diuretics and digoxin for six days without improvement and was referred to us for consideration of aortic valve replacement.

On admission, he was found to be in a poor general condition with features of left heart failure and severe aortic regurgitation. His electrocardiogram showed sinus rhythm and a pattern suggestive of left ventricular hypertrophy. His chest radiograph showed features of pulmonary oedema. Cross sectional echocardiography showed a mildly dilated left ventricle and a normal sized right ventricle with normal contractions. The anatomy of the aortic and mitral valves was normal. In view of his poor condition, he was intubated and ventilated mechanically. Emergency cardiac catheterisation and cineangiocardiography were planned to exclude aortic dissections. During cardiac catheterisation, he went into a low output state and the procedure was abandoned after an aortogram showed a normal ascending aorta and severe aortic regurgitation. He was transferred directly to the operating theatre and put on cardiopulmonary bypass.

At operation, the ascending aorta was normal externally. The aortic wall was thin and appeared to be normal. The aortic valve was tricuspid with normal looking cusps. There was no macroscopic calcification of the aortic valve or at the aortic sinotubular junction. The intact commissure between the left and right coronary cusps was separated from the aortic wall (fig 1). There was no evidence of infective endocarditis or aortic dissections. The aortic valve was replaced with a 27 mm Medtronic-Hall aortic prosthesis. He withstood the operation well and was returned to the intensive care unit in a satisfactory condition. He had one tarry stool on the first postoperative day and endoscopy of the upper

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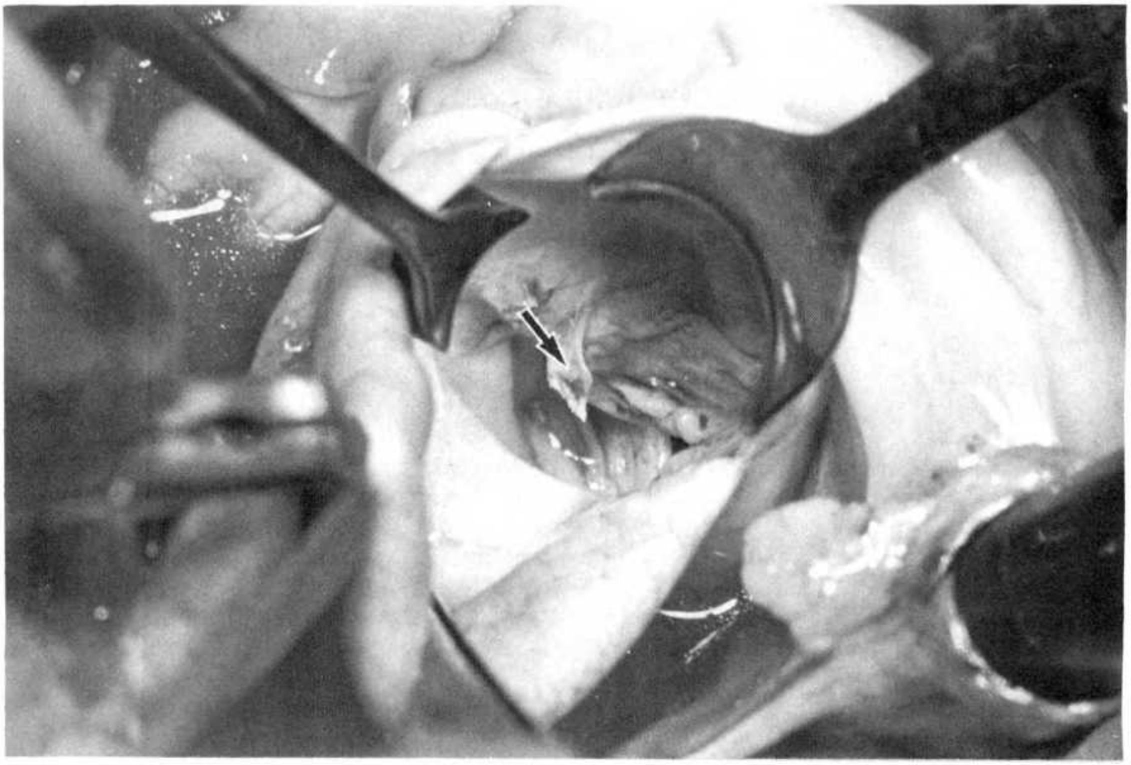

Fig 1 *Photograph at operation showing a normal appearance of aortic root. The intact commissure between the right and left coronary cusps had dehisced from the aortic wall (black arrow). There was no calcification at the aortic sinotubular junction.*

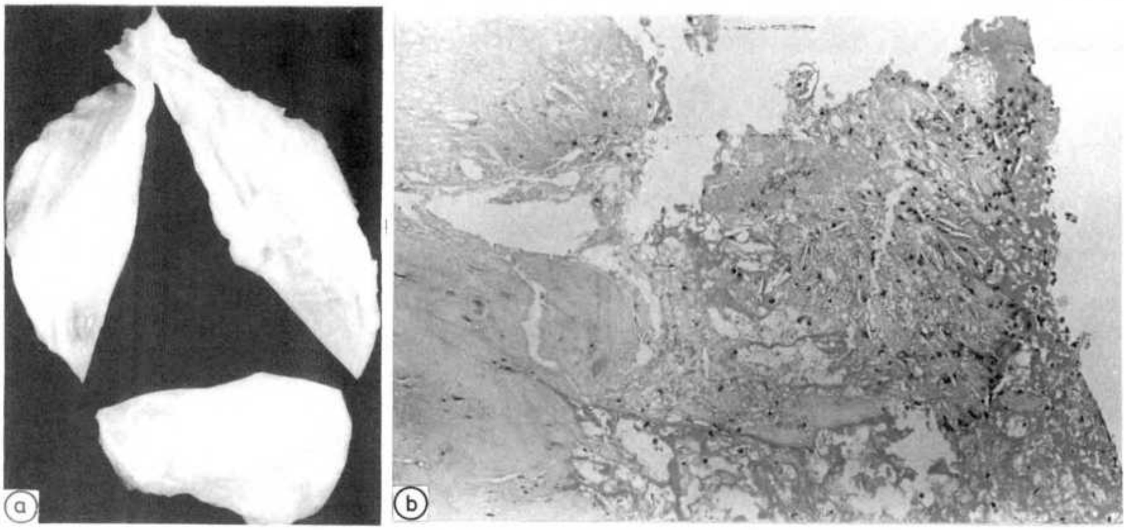

Fig 2 *(a) Macroscopic appearance of the surgically excised aortic valve cusps and the dehisced commissure showing their normal appearance. (b) Microscopic appearance of a section cut perpendicular to the detached commissure. This shows a hyalinised fibrotic mass with an irregular area of lipid deposition, cholesterol clefts, foamy macrophages, and fibroblasts at the ragged edge of the site of separation. Fibrinous masses and small blood clots are also present on the surface. (Haematoxylin and eosin. Original magnification × 100.)*

gastrointestinal tract failed to show the source of bleeding. During the subsequent two days he remained haemodynamically stable with a satisfactory urinary output. Oliguria developed on the fourth postoperative day and peritoneal dialysis had to be started on the fifth postoperative day. He ran a downhill course with features of adult respiratory distress syndrome, hepatic failure, and fulminating septicaemia. He died eight days after aortic valve replacement. Necropsy was refused by his family.

Histopathological examination of the excised aortic valve (fig 2) showed a hyalinised fibrotic mass underneath the commissure between the left and right coronary cusps with an irregular area of lipid deposition, cholesterol clefts, foamy macrophages, and fibroblasts. At the site where the commissure separated from the aortic wall, fibrinous masses and small blood clots were also present on the surface. Calcification or degenerative aortic disease was not seen. Elastic van Gieson stain showed absence of medial elements at the site of dehiscence and evidence that might indicate a localised aortic dissection. Apart from moderate fibrotic thickening and mild patchy mucinous change, the valve cusps showed no abnormality. These features were in keeping with ulceration and rupture of an atheromatous plaque at that site.

Discussion

It is commonly known that atheromatous plaques on the aorta may lead to thinning of the media beneath the plaques; weakening of the aortic wall, and aneurysm formation; or formation of mural thrombus over ulcerated areas, with embolisation to more distal radicles of the arterial system.[4] Detachment of an atheromatous plaque with distal embolisation is also well documented. To the best of our knowledge, however, detachment of an atheromatous plaque leading to aortic regurgitation has not been reported before. The present case shows that this can occur.

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British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 22 to 24 November 1988, and the closing date for receipt of abstracts will be 1 July 1988.

The Annual General Meeting for 1989 will take place in Oxford on 6 and 7 April 1989, and the closing date for receipt of abstracts will be 6 January 1989.

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Thallium scintigraphy in patients with angina at rest

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SUMMARY Sixty six patients with angina at rest were investigated by exercise electrocardiography, thallium scintigraphy, and coronary arteriography. A positive exercise electrocardiogram was highly predictive (93%) but poorly sensitive (52%) of coronary artery disease (≥50% stenosis). Thallium scintigraphy was as predictive of the presence of coronary artery disease (91%) but was also highly sensitive (91%). The diagnostic contribution of the thallium scan was greatest in those patients with an inconclusive exercise electrocardiogram without Q waves.

The investigations recommended for patients with angina at rest vary from the conservative and expectant[1] to the highly invasive.[2] The invasive approach may be appropriate in selected patients referred to specialist cardiology centres after evaluation elsewhere, particularly when there is compelling evidence of ischaemic heart disease. Most clinicians managing rest pain, however, do not have easy access to coronary arteriography. Furthermore, a considerable minority of patients investigated because of chest pain seem to be free of ischaemic heart disease.[3 4] For these reasons and because of the small but real risk in coronary arteriography, a non-invasive test that could be applied widely outside specialist centres to patients with rest pain is attractive. Ideally, such a test would predict accurately the presence or absence of ischaemic heart disease. Thallium scintigraphy at the time of exercise testing is a well established non-invasive test of myocardial perfusion.[5] This study considers its value in the investigation of patients with rest pain.

Patients and methods

In our cardiac unit between August 1982 and July 1983 we examined 124 consecutive patients aged <70 years who were admitted urgently because of angina at rest.[6] In this paper we review the 66 patients who received exercise electrocardiography, thallium scintigraphy, and coronary arteriography.

All patients had spontaneous chest pain at rest that was typical of angina pectoris; they were free of serious intercurrent disease and gave their informed consent. All patients were treated initially with bed rest and conventional medical treatment (nitrates, β blockers, or calcium antagonists) and all became pain free soon after admission.

The treadmill exercise test was symptom limited and followed the Bruce or Naughton-Balke protocol; it was usually performed 3–10 days after admission to hospital. β Blockers were stopped in 20 of 57 patients. In all cases the exercise test was completed safely. The results of the test were regarded as positive if there was ≥1 mm planar or downsloping ST segment depression in three consecutive complexes or ≥1 mm depression of an upsloping ST segment 80 ms after the J point; as negative if 95% of the maximum predicted heart rate was attained without diagnostic ST segment change; and as inconclusive if the patient failed to attain 85% of the maximum predicted heart rate in the absence of a diagnostic change in the ST segment.

The thallium scintigraphy was performed in combination with the exercise test in all cases. About one minute before maximum stress 55·5 MBq thallium-201 was injected into an arm vein. After six minutes' rest, images were obtained consecutively in the anterior, left anterior oblique 45°, and left anterior oblique 70° projections. The images were collected for 10 minutes in each projection by an Ohio 420 mobile gammacamera with a high resolution collimator with a 25% window centred on the 80 keV peak. Late images were collected in the same way two and a half hours later. All images were stored on floppy discs and interpreted later by two experienced observers who were unaware of the diagnosis. The images were said to be positive (reperfusion, fixed defect, or both) or negative (no defect). If the two

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R J E Lee held a Royal Victoria Hospital Research Fellowship.

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observers did not agree a third observer also analysed the images.

Coronary arteriography with left ventriculography was carried out according to Judkins' technique not more than three months after the non-invasive tests. No new cardiac event occurred in the interim. No adverse events were associated with the procedure. The studies were interpreted blindly by one observer. A study was said to be positive for coronary artery disease when there was a ≥50% stenosis in a major vessel or a major branch of a major vessel.

Results

We studied 48 men and 18 women (mean age 55 (range 35–69) years). Fifty eight patients had had previous episodes of angina and 24 had electrocardiographic Q waves.

EXERCISE ELECTROCARDIOGRAPHY

Thirty (45%) patients had a positive exercise electrocardiogram, six (10%) a negative test, and 30 (45%) an inconclusive test.

THALLIUM SCINTIGRAPHY

Thallium scintigraphy was positive in 54 (82%) and negative in 12 (18%) patients.

CORONARY ARTERIOGRAPHY

Coronary artery disease (≥50% stenosis) was present in 54 (82%) patients—15 single, 17 double, and 20 triple vessel disease. A further two patients had left main stem stenosis with triple vessel disease. Of 12 patients with normal coronary arteries, four had another lesion detected by ventriculography: one left ventricular hypertrophy, one hypertrophic obstructive cardiomyopathy, and two mitral valve prolapse.

EXERCISE ELECTROCARDIOGRAPHY VERSUS CORONARY ARTERIOGRAPHY (Table 1)

The arteriogram was positive in 28 of the 30 patients with a positive exercise electrocardiogram, in two of the six patients with a negative exercise electrocardiogram, and in 24 of the 30 patients with an inconclusive exercise electrocardiogram. Thus the sensitivity of the exercise electrocardiogram for coronary artery disease was 52% (95% confidence interval 39%–65%) and its specificity was 33% (95% confidence interval 6%–50%). The predictive accuracy of a positive exercise electrocardiogram for the presence of coronary artery disease was 93% (95% confidence interval 84%–100%). The predictive accuracy of a negative exercise electrocardiogram for the absence of coronary artery disease was 67% (95% confidence interval 29%–100%).

THALLIUM SCINTIGRAPHY VERSUS CORONARY ARTERIOGRAPHY (table 1)

The arteriogram was positive in 49 of the 54 patients with a positive thallium scan and in five of the 12 patients with a negative scan. Thus the sensitivity of the thallium scan for coronary artery disease was 91% (95% confidence interval 83%–100%) and the specificity was 58% (95% confidence interval 30%–86%). The predictive accuracy of a positive scan for the presence of coronary artery disease was 91% (95% confidence interval 83%–99%). The predictive accuracy of a negative scan for the absence of coronary artery disease was 58% (95% confidence interval 30%–86%).

β BLOCKADE AND THE EXERCISE ELECTROCARDIOGRAM

Thirty seven patients were receiving β blockers at the time of exercise testing. Of these, 17 (46%) had a positive exercise electrocardiogram, two (5%) a negative test, and 18 (49%) an inconclusive test. Of the 26 patients not on β blockers at the time of testing, 11 (38%) had a positive exercise electrocardiogram, three (11%) a negative test, and 12 (46%) an inconclusive test. We do not know whether three patients were or were not taking β blockers at the time of testing.

There was no significant difference in the proportion of patients with a definite exercise electrocardiogram result on or off β blockers.

OUTCOME OF TESTING IN PATIENTS WITH AND WITHOUT Q WAVES

Patients with abnormal Q waves

Of the 24 patients with abnormal Q waves on their resting electrocardiogram, 11 (46%) had a positive exercise electrocardiogram, one (4%) a negative test, and 12 (50%) an inconclusive test. All but one patient (who had a positive exercise electrocardiogram) had a positive thallium scan and all 24 patients had a

Table 1 *Results of exercise electrocardiography, thallium scintigraphy, and coronary arteriography in 66 patients with angina at rest*

	Exercise electrocardiography					
	Positive (30)		*Inconclusive (30)*		*Negative (6)*	
	Pos	*Neg*	*Pos*	*Neg*	*Pos*	*Neg*
Thallium scintigraphy	25	5	25	5	4	2
Coronary arteriography						
Positive	24	4	23	1	2	0
Negative	1	1	2	4	2	2
Totals	25	5	25	5	4	2

positive arteriogram: four single vessel, eight double vessel, 11 triple vessel, and one left main stem stenosis (with triple vessel disease) (table 2).

The sensitivity of the exercise electrocardiogram for coronary artery disease was 46% (95% confidence interval 36%–56%) and the specificity was 0%. The predictive accuracy of a positive exercise electrocardiogram for the presence of coronary disease was 100%, and the predictive accuracy of a negative test for the absence of disease was 0%.

The sensitivity of the thallium scan for coronary artery disease was 96% (95% confidence interval 88%–100%) and its specificity was 0%. The predictive value of a positive thallium scan for the presence of coronary disease was 100%, and that of a negative scan for the absence of disease was 0%.

Patients without abnormal Q waves

Of the 42 patients without abnormal Q waves on their resting electrocardiogram, 19 (45%) had a positive exercise electrocardiogram, five (12%) had a negative test, and 18 (43%) had an inconclusive test. There were 31 (74%) patients with a positive thallium scan and 11 (26%) with a negative scan. Thirty patients had coronary artery disease: 11 single vessel, nine double vessel, nine triple vessel, and one left main stem stenosis (with triple vessel disease) (table 3).

The sensitivity of the exercise electrocardiogram for detecting coronary artery disease was 57% (95% confidence interval 48%–66%) and its specificity was 33% (95% confidence intervals 5%–60%). The predictive value of a positive exercise electrocardiogram for coronary disease was 89% (95% confidence interval 82%–96%). The predictive value of a negative exercise electrocardiogram for the absence of coronary disease was 80% (95% confidence interval 63%–97%).

The sensitivity of the thallium scan for coronary artery disease was 87% (95% confidence interval 81%–93%) and its specificity was 58% (95% confidence interval 44%–72%). The predictive accuracy of a positive scan for the presence of coronary disease was 84% (95% confidence interval 77%–91%). The predictive accuracy of a negative scan for the absence of coronary disease was 64% (95% confidence interval 49%–79%).

In the subgroup of patients without Q waves and with an inconclusive exercise electrocardiogram the thallium scan had a sensitivity for coronary disease of 92% (95% confidence interval 84%–100%). The specificity was 66% (95% confidence interval 47%–85%). The predictive value of a positive scan for coronary disease was 85% (95% confidence interval 75%–95%). The predictive value of a negative scan for the absence of disease was 80% (95% confidence interval 62%–98%).

Discussion

Up to 30% of patients with typical cardiac chest pain do not have ischaemic heart disease.[4] For this reason investigation of such patients to confirm or exclude a cardiac aetiology is important. It is perhaps self evident that Q waves on the electrocardiogram are diagnostic of ischaemic heart disease and such was the case in this study. Even when this clue is present, an exercise test is often arranged to assess exercise capacity, the degree and direction of ST segment shift, or the presence of ventricular extrasystoles. Also although thallium scintigraphy may be performed at rest[7] or during rest pain,[8] the best results are obtained with exercise.[5]

Nixon *et al* have shown that submaximal exercise testing is useful and safe in the evaluation of unstable angina.[9] In our study maximum exercise testing was performed safely in all patients. Some patients were taking β blockers, but there was no significant difference in the proportion of conclusive exercise

Table 2 *Results of exercise electrocardiography, thallium scintigraphy, and coronary arteriography in 24 patients with angina at rest and Q waves*

	Exercise electrocardiography					
	Positive (11)		*Inconclusive (12)*		*Negative (1)*	
	Pos	*Neg*	*Pos*	*Neg*	*Pos*	*Neg*
Thallium scintigraphy	10	1	12	0	1	0
Coronary arteriography						
Positive	10	1	12	0	1	0
Negative	0	0	0	0	0	0
Totals	10	1	12	0	1	0

Table 3 *Results of exercise electrocardiography, thallium scintigraphy, and coronary arteriography in 42 patients with angina at rest and no Q waves*

	Exercise electrocardiography					
	Positive (19)		*Inconclusive (18)*		*Negative (5)*	
	Pos	*Neg*	*Pos*	*Neg*	*Pos*	*Neg*
Thallium scintigraphy	15	4	13	5	3	2
Coronary arteriography						
Positive	14	3	11	1	1	0
Negative	1	1	2	4	2	2
Totals	15	4	13	5	3	2

electrocardiograms obtained in those patients who were taking β blockers and those who were not.

We found that a positive exercise test was highly predictive of ischaemic heart disease (93%) and that to a lesser degree (67%) a negative test predicted the absence of ischaemia. In these patients the thallium scintigram contributed little diagnostic information. A sizeable minority of patients with an inconclusive exercise test (30, 45%) remained. In these patients the thallium scan predicted the presence or absence of ischaemic heart disease in 27 (90%) of the 30 patients. In the 18 patients with an inconclusive exercise electrocardiogram without Q waves the thallium scan predicted the presence or absence of ischaemic heart disease in 15 (83%).

We conclude that maximal exercise testing may be performed safely in patients with rest pain soon after stabilisation on medical treatment. Thallium scintigraphy is a valuable diagnostic adjunct to the exercise electrocardiogram especially in those patients with inconclusive exercise tests and without electrocardiographic Q waves.

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The dobutamine stress test as an alternative to exercise testing after acute myocardial infarction

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SUMMARY Three weeks after myocardial infarction in 50 patients the effect of the infusion of a graded dose of dobutamine was compared with that of symptom limited treadmill exercise testing. The following variables were measured: blood pressure, heart rate, ST segment changes, Doppler aortic blood flow, and cross sectional echocardiographic dimensions. The heart rate and double product increased more during exercise than during dobutamine infusion, while maximum acceleration in the ascending aorta increased more during dobutamine infusion than during exercise. Significant ST depression was recorded in 22 patients during exercise and in 24 during dobutamine infusion; the concordance between the two tests was 88%. In all cases in which ST segment depression occurred in both tests the site of ST depression was the same. Dobutamine stress testing is an alternative to exercise testing in patients after myocardial infarction.

Exercise stress testing has an established place in the assessment of patients after acute mycardial infarction.[1] Many patients complete an exercise test without difficulty and gain encouragement from their performance. A sizeable minority, however, are not able to perform an adequate test because of anxiety, poor motivation, peripheral vascular disease, or musculoskeletal or neurological disorders. Furthermore, imaging techniques such as echocardiography cannot usually be performed satisfactorily during exercise.

Methods other than exercise have been developed to induce ischaemia in patients with ischaemic heart disease, including dipyridamole thallium imaging,[2 3] atrial pacing,[4] and inotropic stimulation with isoprenaline, dopamine, or dobutamine.[5–7] Few reports, however, examine the value of inotropic stimulation as a method of testing for residual ischaemia in patients after infarction.

We have studied the electrocardiographic and haemodynamic effects of graded doses of intravenous dobutamine in patients early after acute myocardial infarction and have compared these changes with those occurring during exercise testing in the same patients.

Patients and methods

PATIENTS

Exercise and dobutamine stress tests were performed three weeks after acute myocardial infarction in fifty patients (mean (SD) age 56 (5), range 35–69). Nine (18%) of the patients were women. The diagnosis of acute myocardial infarction was based on at least two of three criteria: (*a*) a history of chest pain suggestive of myocardial ischaemia persisting for at least 30 minutes; (*b*) evolution of new pathological Q waves or persistent ST-T wave changes suggestive of non-Q wave infarction; (*c*) a rise in the concentrations of aspartate transaminase, hydroxybutyrate dehydrogenase, or creatine kinase to at least twice the upper limits of the reference ranges. The resting electrocardiogram showed anterior infarction in 16 patients, inferior in 22, lateral in four, true posterior in two, and non-Q wave infarction in six. Three (6%) patients had a history of a previous myocardial infarction. Patients with bundle branch block or non-ischaemic valvar heart disease were excluded. Patients were randomly selected for the study before the exercise test and their written consent was obtained.

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EXERCISE STRESS TESTING

Three weeks after myocardial infarction patients performed symptom limited treadmill exercise testing according to the Bruce protocol. A 12 lead electrocardiogram was recorded before exercise, at the end of each stage, and at peak exercise. Leads II, V2, and V5 were monitored continuously. Blood pressure was measured in the right arm by sphygmomanometry at the same time as the electrocardiogram was recorded. The double product, heart rate × systolic blood pressure, was calculated at rest and at peak exercise. A positive test was defined by the development of $\geqslant 1$ mm of horizontal or downsloping ST segment depression 80 ms after the J point in any lead except aVR.

Stroke volume and cardiac output were determined by transcutaneous continuous wave Doppler ultrasound and M mode echocardiography as previously described.[8] Blood flow in the ascending aorta was measured from the suprasternal notch by a bidirectional continuous wave Doppler blood velocity meter (Bach Simpson BVM 202 transmitting at 2·2 MHz or Quinton Exerdop transmitting at 3·0 MHz) The systolic velocity integral and the maximum acceleration were obtained from the aortic blood velocity signals recorded at rest and at peak exercise.[9] The cross sectional area of the aortic root was measured at rest by M mode echocardiography. The average systolic aortic root diameter was determined from the M mode recordings by planimetry.[10]

Exercise was continued until one of the following end points developed: (*a*) >3 mm ST segment depression 80 ms after the J point; (*b*) a fall in the systolic blood pressure of >10 mmHg; (*c*) the development of chest pain, dyspnoea, fatigue, dizziness, or leg cramps.

DOBUTAMINE STRESS TESTING

Dobutamine stress testing was undertaken on the day after the exercise test. After a control period dobutamine was infused via an intravenous cannula placed in a vein in the left forearm. We increased the dose from 5 μg/kg/min up to a maximum of 20 μg/kg/min in steps of 5 μg/kg/min. Six to eight minutes after the start of each dose we recorded a 12 lead electrocardiogram, blood pressure, and Doppler aortic blood flow measurements.

Cross sectional echocardiographic studies were performed during the control period and during the peak dobutamine infusion rate with a Xonics 5500D or Hewlett-Packard 77020A system with a 3·5 MHz transducer. Whenever possible, multiple images were obtained in the parasternal long axis and short axis (mitral valve and papillary muscle levels) views and the apical two and four chamber views. Images were recorded on to video tape and were analysed by an expert independent observer who was unaware of the other test findings. For quantitative analysis the left ventricle was divided into 16 segments according to a modified version of the convention described by Gibson *et al.*[11] Segmental wall motion was determined by the observer's impression of the inward movement of the endocardium and the degree of myocardial thickening during systole. Each wall segment was assigned a number corresponding to the wall motion analysis: -1 = hyperkinetic, 0 = normal, 1 = hypokinetic, 2 = akinetic, and 3 = dyskinetic. The sum of the segmental scores was divided by the number of segments seen and a wall motion score index was thus derived. For the study to be regarded as acceptable, the same segments had to be imaged both at rest and during stress.

Dobutamine infusion was continued until one of the following end points: (*a*) development of $\geqslant 3$ mm ST segment depression, (*b*) development of chest pain or dyspnoea, (*c*) development of frequent or complex ventricular arrhythmias, (*d*) attainment of the peak dose (20 μg/kg/min).

Patients stopped taking β blocking agents for at least 48 hours before the exercise test. Patients taking calcium antagonists, nitrates, or diuretics continued their medication throughout the studies.

CARDIAC CATHETERISATION

Cardiac catheterisation was carried out by either the Judkins' or Sones' technique within four weeks of the stress tests in 26 patients in whom there was a clinical indication for catheterisation (post-infarction angina, ST depression on exercise, or poor blood pressure response to exercise). The angiograms were evaluated by an experienced observer who was unaware of the other test findings. Disease was regarded as significant if there was a stenosis of $\geqslant 50\%$ in the left mainstem coronary artery or $\geqslant 70\%$ in the other vessels. Disease in the branches of left anterior descending, circumflex, and right coronary arteries was classified as disease of the main vessel.

STATISTICAL ANALYSIS

Two tailed Student's *t* tests, paired when appropriate, were used to test for statistically significant differences in the continuous variables that we measured. The χ^2 test was used for discrete variables. The mean and standard errors of the mean are shown; a value of at least $p < 0.05$ was regarded as significant.

Results

HAEMODYNAMIC RESPONSES

Technically acceptable Doppler studies of aortic blood velocity were obtained in 38 patients during exercise and dobutamine administration. The table shows the haemodynamic responses to exercise and dobutamine. Systolic blood pressure, heart rate, double product, maximum acceleration, and cardiac output at peak exercise and peak dobutamine infusion rates were significantly higher than control values. Peak exercise produced a significantly greater increase in heart rate than peak dobutamine (68% *vs* 44%, $p<0{\cdot}001$) Similarly, peak exercise produced a greater increase in double product than peak dobutamine (107% *vs* 77%, $p<0{\cdot}001$). In contrast, the increase in maximum acceleration in the ascending aorta was significantly greater with dobutamine than with exercise (118% *vs* 51%, $p<0{\cdot}001$).

ST SEGMENT CHANGES

Significant ST segment depression was recorded in 22 patients during exercise and in 24 during dobutamine infusion; the concordance between the two tests was 88% ($p<0{\cdot}01$):

		Dobutamine	
		−ve	+ve
Exercise	−ve	24	4
	+ve	2	20

In all cases in which ST segment depression occurred in both tests, the site of ST depression was the same. ST segment depression started in one patient at 5 μg/kg/min, in 10 at 10 μg/kg/min, in 10 at 15 μg/kg/min, and in three at 20 μg/kg/min of dobutamine. The heart rate at the onset of important ST segment depression was significantly lower for dobutamine (93 (4) min) than for exercise (117 (6) min) ($p<0{\cdot}01$). No patient had downsloping ST depression on dobutamine, though two patients developed downsloping ST depression during the recovery phase after exercise. In 10 patients with an exercise time of less than three minutes, 7 (70%) also failed to reach the maximum dobutamine dose because of chest pain or ST depression. Fifteen (94%) of the 16 patients who developed significant ST depression before three minutes of exercise again failed to reach the maximum dobutamine dose because of ST depression.

WALL MOTION ABNORMALITIES DURING DOBUTAMINE INFUSION

Technically acceptable cross sectional echocardiograms were obtained during control tests and at peak dobutamine infusions in 41 patients. In 20 patients the wall motion score index was higher at peak dobutamine infusion than during the baseline test, indicating increased wall motion abnormality. There was a significant association between the change in wall motion score index (WMSI) and the presence of significant ST segment depression at peak exercise ($p<0{\cdot}01$).

	WMSI less	*WMSI same or more*
No ST segment depression	17	4
ST segment depression	3	17

In patients with no ST segment changes mean wall motion score index was lower at peak dobutamine infusion (0·44 (0·13)) than at baseline (0·71 (0·08)), $p<0{\cdot}01$. In patients with significant ST depression, there was an increase in mean wall motion score index, though this did not reach statistical significance (0·80 (0·12)) at peak dobutamine *vs* 0·63 (0·12) baseline). Three of the four patients with no ST segment depression but an increase in wall motion score index had widespread electrocardiographic abnormalities at rest caused by multiple previous infarctions.

CATHETERISATION DATA

Catheterisation data were available in 25 patients. Thirteen had three vessel disease, six had two vessel disease, and six had single vessel disease. Three of the patients with triple vessel disease had no significant ST changes during the dobutamine test; the remaining ten all showed a positive electrocardiographic response to dobutamine. All three patients with triple vessel disease but without ST changes on

Table *Haemodynamic data (mean (SE)) during exercise and dobutamine infusion in 38 patients three weeks after acute myocardial infarction*

	Exercise		*Dobutamine*		*p value for comparison between exercise and dobutamine tests*	
Data	*Rest*	*Peak*	*Control*	*Peak*	*Rest*	*Peak*
Systolic BP (mm Hg)	122 (3·3)	150 (4·6)*	127 (2·9)	153 (5·8)*	NS	NS
Heart rate (beats/min)	81 (2·5)	136 (3·6)*	78 (2)	112 (3·6)*	NS	<0·001
Double product (mm Hg/min × 10^{-2}	99·6 (3·9)	206·4 (8·9)*	95·5 (3·0)	169 (6·9)*	NS	<0·001
Maximum acceleration (ms^{2})	15·9 (0·7)	24·1 (4·0)*	17·3 (0·7)	37·7 (3·3)*	NS	<0·001
Stroke volume (ml)	68 (3·7)	63 (4·6)	77·0 (4·7)	74·4 (3·9)	<0·05	<0·05
Cardiac output (l/min)	5·0 (0·3)	8·5 (0·7)*	6·0 (0·4)	7·8 (0·5)*	<0·01	NS

*$p<0{\cdot}05$ for comparison between resting and peak values.

dobutamine had widespread electrocardiographic abnormalities at rest, and in all three there was a striking increase in wall motion abnormality shown by echocardiography during dobutamine stress, with a mean increase in wall motion score of 50%, compared with a 175% decrease in wall motion score in those patients without ST depression who did not have three vessel disease. The increase in blood pressure during dobutamine was significantly smaller in those with three vessel disease than in those known to have two or one vessel disease (10 (15) *vs* 26 (17) mm Hg, $p < 0{\cdot}02$).

ADVERSE REACTIONS AND COMPLICATIONS

Neither exercise nor dobutamine infusion caused any serious complications or adverse reactions. Five patients experienced angina on exertion during exercise.

Dobutamine infusion was stopped before 20 μg/kg/min in 20 patients for the following reasons: a sensation of pounding in the head in four (at 15 μg/kg/min); chest pain in one (at 5 μg/kg/min); nausea in one (10 μg/kg/min); shortness of breath in two (at 10 and 15 μg/kg/min); maximum heart rate for age and sex in three (at 15 μg/kg/min); systolic blood pressure >200 mm Hg in one (at 15 μg/kg/min); 3 mm ST segment depression in three (one at 10 and two at 15 μg/kg/min); frequent or complex ventricular extrasystoles in two (at 15 μg/kg/min); and >3 mm ST segment depression and complex extrasystoles in three (at 10 μg/kg/min). The onset of important ventricular extrasystoles started during dobutamine administration in eight patients; one patient had non-sustained uniform ventricular tachycardia of ten beats, four patients developed occasional ventricular couplets, and three developed >10 ventricular extrasystoles/minute at the peak dose. In seven out of the 50 patients the frequency of extrasystoles increased on exercise, but none had ventricular tachycardia. In no patient in whom the results of exercise and dobutamine were discordant with respect to ST depression was either test stopped because of adverse effects other than ST depression or chest pain. In all cases, the effects of dobutamine, in terms of heart rate, blood pressure, ST depression, and adverse effects (where these occurred) subsided very quickly, within one minute in most cases, without further treatment once the infusion was stopped.

Discussion

ST depression on exercise[1] and the haemodynamic response to exercise[12-14] are valuable in the detection of multivessel disease and in predicting mortality in patients after acute myocardial infarction. The value of the exercise test is, however, limited in a substantial minority of patients by anxiety or pre-existing musculoskeletal, neurological, or pulmonary disease. The value of the test is also limited in those with widespread electrocardiographic abnormalities at rest, because in these patients the electrocardiographic changes may be modified, and imaging techniques are difficult to perform during exercise. While several alternative and often excellent techniques have been developed to allow stress testing and cardiac imaging without exercise in patients with ischaemic heart disease, including the dipyridamole-thallium test,[2 3] exercise radionuclide ventriculography,[12-14] and atrial pacing-echocardiography,[4] these tests are not widely used because of the specialised equipment and expertise that they require. Such tests cannot usually be performed in the district general hospital, to which most patients with acute myocardial infarction are admitted. The advantage of the test that we have described is that it requires only simple, familiar equipment. In nearly all of our patients, there was concordance between the occurrence of ST changes on dobutamine and during exercise, and so the tests may be regarded as providing similar information.

We also found that, although this was not an essential part of the test, in some patients echocardiography could be performed easily during dobutamine infusion and did provide extra information: in the three patients without significant ST changes during dobutamine in whom triple vessel disease was demonstrated, there was a striking increase in wall motion abnormality during dobutamine infusion. In these three patients any ST changes on exercise were obscured by widespread ST abnormalities at rest caused by previous infarction; dobutamine infusion with echocardiography may thus provide a non-invasive technique for identifying three vessel disease in such patients. It must be emphasised, however, that in many patients detailed echocardiographic analysis of wall motion is not feasible and also that assessment of wall motion is subjective. Considerable expertise is needed to detect small changes in wall motion and such changes are probably not reliable enough to be of much value in practice. In cases in which there are considerable changes, however, useful conclusions may be drawn. The dobutamine stress test may also prove to be of value when combined with other forms of cardiac imaging, such as radionuclide studies.

Although the use of inotrope infusion tests to induce myocardial ischaemia in patients with ischaemic heart disease has been reported before,[5 7] experience in the early post-infarction period is limited. Berthe *et al* have recently shown that cross sectional echocardiography with dobutamine testing was better than pre-discharge submaximal bicycle exercise testing for the detection of three vessel disease after infarction.[15]. We found that the dobutamine test was also of value three weeks after acute infarction when symptom limited treadmill exercise was performed.

We were able to examine in more detail the mechanism of ischaemia during dobutamine infusion. The double product was lower during dobutamine administration since although the systolic blood pressure increased to a comparable extent, the increase in heart rate was less on exercise. Maximum acceleration, on the other hand, increased to a much greater extent during dobutamine infusion than during exercise. The ischaemia produced during dobutamine infusion therefore seems to be caused predominantly by an increase in the inotropic state rather than through an increase in heart rate (as it is during exercise). In this small study we have not been able to assess fully the ability of the dobutamine stress test to assist in distinguishing between patients with triple vessel disease and those with single and double vessel disease in the same way in which this is sometimes possible with exercise.[16] None the less, as with exercise testing, those with triple vessel disease did have a smaller increase in blood pressure during the dobutamine test than those without three vessel disease. Furthermore, the only patient with very early onset ST depression on dobutamine had severe three vessel disease; but none of those in whom ST depression occurred late (at a dose of 20 μg/kg/min) had triple vessel disease. Seven out of the ten patients who were unable to complete more than three minutes of exercise also developed ischaemia before the maximum dobutamine dose, and fifteen of the sixteen patients who developed ST depression within the first three minutes of exercise developed ischaemia before the maximum dose of dobutamine was reached. No downsloping ST depression was seen with dobutamine, though this could have been partly because the effects of dobutamine were more short lived than the effects of exercise, so that the same degree of ischaemia did not develop. Although a larger study would be needed to establish the discriminatory power of the dobutamine test for identification of three vessel disease, these preliminary results suggest that the dobutamine test would be at least as good as exercise.

In conclusion, we found that the use of graded doses of dobutamine infusion in patients three weeks after myocardial infarction produced changes in ST segment and blood pressure that resembled those that occurred on treadmill exercise. It seems that ischaemia is induced by increased inotropism during this test, despite the smaller increase in heart rate than on exercise. The test is economical and requires only familiar, widely available equipment. Some arrhythmias are induced, however, so that the test may not be suitable in patients with a tendency to arrhythmia; full resuscitation facilities should be available when the test is performed. Dobutamine stress testing is a possible alternative to exercise testing in patients after myocardial infarction.

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Cost benefit analysis of early thrombolytic treatment with intracoronary streptokinase

Twelve month follow up report of the randomised multicentre trial conducted by the Interuniversity Cardiology Institute of The Netherlands

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SUMMARY The costs and benefits of early thrombolytic treatment with intracoronary streptokinase in acute myocardial infarction were compared in a randomised trial. All hospital admissions were recorded and the functional class was assessed at visits to the outpatient clinic during a 12 month follow up of 269 patients allocated to thrombolytic treatment and of 264 allocated to conventional treatment. Mean survival during the first year was calculated for patients with inferior and with anterior infarction and adjusted for impaired quality of life in cases where there were symptoms or hospital admission. In patients with inferior infarction mean survival was 337 days (out of a total follow up of 365 days) for patients allocated to thrombolytic treatment and 327 days for controls. Quality adjusted survival was seven days longer in the thrombolysis group (307 *vs* 300 days in controls). In patients with anterior infarction mean survival was significantly longer (35 days) in the thrombolysis group than in the control group as was quality adjusted survival (38 days) (304 *vs* 266 days in controls). The gain in life expectancy with thrombolytic treatment was 0·7 years for patients with inferior infarction, 2·4 years for patients with anterior infarction, and 3·6 years for the subset of patients with large anterior infarction who were admitted within two hours of the onset of symptoms. The costs of medical treatment, including medication, hospital stay, cardiac catheterisation, coronary angioplasty, and bypass surgery, in the first year follow up were higher in patients allocated to thrombolytic treatment (an additional cost of Dfl 7000 in inferior and Dfl 9000 in anterior infarction (£1 ≏ Dfl 3·3)) than in conventionally treated patients. The additional costs per year of life gained were Dfl 10 000 in inferior infarction, Dfl 3 800 in anterior infarction, and only Dfl 1 900 in patients with large anterior infarction admitted within two hours of onset of symptoms.

Intracoronary thrombolysis can be recommended as a cost effective treatment in patients with extensive anteroseptal infarction.

In the randomised trial conducted by the Netherlands Interuniversity Cardiology Institute, patency of the infarct related coronary artery was achieved in 85% of the patients treated with intracoronary streptokinase. This result was associated with limitation of enzymatic infarct size, improvement of global and regional left ventricular function, and improved survival.[1-6] Non-fatal reinfarction, however, occurred more frequently and percutaneous transluminal coronary angioplasty or coronary artery bypass grafting were required more

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often in patients allocated to thrombolytic treatment than in the control group.[1 2] The improved survival after early thrombolytic treatment on one hand and the higher incidence of non-fatal complications in these patients make it difficult to assess the true value of thrombolytic treatment in acute myocardial infarction. To obtain a complete picture of total mortality and morbidity the functional status of each patient was recorded at regular intervals during one year follow up. Also the total medical costs were recorded for each patient. From these data mean survival was calculated and adjusted for impaired quality of life when there were symptoms or hospital admission. The additional costs of thrombolytic treatment per year of life gained were also calculated.

Patients and methods

Five hundred and thirty three patients entered the trial as described in an earlier report.[1] Patients were eligible for the trial if they were admitted to one of the five participating coronary care units within four hours of the onset of chest pain with electrocardiographic signs that were typical of myocardial infarction. Two hundred and sixty four patients were allocated to conventional treatment and 269 to thrombolytic treatment. Of the latter patients, 152 were allocated to intracoronary streptokinase and 117 to intracoronary streptokinase preceded by intravenous streptokinase. Patients allocated to thrombolytic treatment were asked for their informed consent. Patients who refused consent or patients in whom thrombolytic treatment was withheld for other reasons received conventional treatment, but were included in the analysis on the basis of the intention to treat.[7] Acute coronary angiography was performed in 234 patients allocated to thrombolytic treatment. If the infarct related coronary artery appeared to be occluded, intracoronary streptokinase (usually 250 000 U) was given. In the second part of the study intravenous streptokinase (500 000 U) was given before angiography to reduce treatment delay. In 46 patients with severe residual stenosis of the infarct related coronary artery, coronary angioplasty was attempted as part of the recanalisation procedure. After catheterisation patients allocated to thrombolytic treatment had the same treatment protocol as the control group.[1] The location of the infarct was defined as anterior if there was ST segment elevation in leads V1 to V4 and as inferior if there was ST segment elevation in leads II, III, and aVF. When there was ST segment elevation in leads I, aVL, V5 and V6, the infarct was defined as anterior, unless ST segment elevation was also present in leads II, III, and aVF or ST segment depression was present in leads V1 to V4. In the latter case the infarct was defined as inferior. The ΣST on the electrocardiogram was defined for anterior infarcts as the sum of ST segment elevation in leads I, aVL, and V1 to V6 and that for inferior infarcts was defined as the sum of ST segment elevation in leads I, II, III, aVL, aVF, V5 and V6, and ST segment depression in leads V1 to V4.[6]

All patients were followed at the outpatient clinic for at least a year after admission. The following data were recorded:

(*a*) functional class (New York Heart Association) on the day of each visit to the outpatient clinic[8];
(*b*) all hospital admissions, including day of admission, day of discharge, and reason for admission;
(*c*) functional class before hospital admission and functional class at discharge; and
(*d*) day and cause of death and functional class before death (if a patient died).

From these data the functional state of each patient was defined every week as the lowest of mutually exclusive classifications: class I (New York Heart Association criteria), not in hospital; class II, not in hospital; class III, not in hospital; class IV, not in hospital; in hospital; or dead.

Functional class was assumed to have changed halfway between two subsequent visits to the outpatient clinic unless known otherwise. The mean number of days spent in each category was calculated for all patients. Mean survival was calculated for each group of patients as the mean time between admission to the study and death or the end of follow up (one year). Survival was adjusted for impaired quality of life according to the number of days spent in class II–IV or in hospital, as described in the results.[9] Life expectancy was estimated by the "DEALE" method.[10 11] The mortality rate was assumed to be 6% per year for patients alive at the end of follow up. Mean life expectancy was calculated for subsets of patients in both treatment groups as the interval from admission to the study to death for those who died during follow up and as 16·7 years (mean survival at a mortality rate of 6% per year) plus the duration of follow up for those who were alive at the end of follow up.

The costs of medical treatment the first year after acute myocardial infarction were calculated, taking into account the number of days in hospital, the increased costs for stay in a coronary care unit or surgical intensive care unit, costs of acute coronary angiography including thrombolytic treatment with or without coronary angioplasty, costs of elective coronary angiography, elective coronary angioplasty, bypass surgery, and medication as prescribed at discharge or at the outpatient clinic. The costs of medication were based on average dosages of antiarrhythmic drugs, platelet inhibitors, β blockers, cal-

Table 1 *Baseline and follow up data in a trial of intracoronary streptokinase*

	All patients			*Inferior MI*			*Anterior MI*		
	C	*T*	*p**	*C*	*T*	*p**	*C*	*T*	*p**
Number of patients	264	269		148	139		116	130	
Men	224	217		123	110		101	107	
Age (median)	56	57		57	58		55	56	
Previous myocardial infarction	60	56		31	28		29	28	
Median admission delay (min)	90	90		90	90		90	90	
Median cumulative HBDH release (U/l)	1100	770	0·0001	970	670	0·007	1280	840	0·005
Mean angiographic LVEF (day 10–40 (%))	47	53	0·0001	49	57	0·0001	43	50	0·002
Total one year mortality	43	26	0·03	17	12	0·4	26	14	0·01
Recurrent myocardial infarction	14	36	0·001	9	26	0·001	5	10	0·3

MI, myocardial infarction, C, control group, T, thrombolysis group, HBDH, α hydroxybutyrate dehydrogenase, LVEF, left ventricular ejection fraction *Two tailed p values (Mann-Whitney's rank sum test or Fisher's exact text).

cium antagonists, digoxin, diuretics, nitrates, other vasodilators, and the costs of anticoagulation treatment including regular coagulation tests.

Differences between groups were tested by Fisher's exact test, Mann-Whitney's rank sum test, or Student's *t* test when appropriate. Two tailed p values are reported.

Results

One year follow up was complete in all 533 patients admitted to the trial, and the duration of follow up ranged from one to four years (mean two years). Baseline characteristics were distributed evenly between both treatment groups (table 1). Patients allocated to thrombolytic treatment showed a 30% limitation of infarct size estimated enzymatically (median hydroxybutyrate dehydrogenase release 770 U/l *vs* 1100 U/l in controls, p = 0·0001), higher left ventricular ejection fraction by contrast angiography (53% *vs* 47%, p = 0·0001), improved one year survival (90% *vs* 84%, p = 0·03), and a higher incidence of non-fatal reinfarction (13% *vs* 5%, p = 0·001). Mean hospital stay during the first year was similar in both treatment groups, although coronary angioplasty and bypass surgery were performed more frequently in the thrombolysis group (table 2).

Figure 1 shows the proportion of patients in each functional class at weekly intervals during one year follow up. The survival of patients allocated to thrombolytic treatment was greater than that of the control group as is evident by the larger area occupied by the survivors. The mean survival and average number of days spend in each category were calculated (table 3). In the thrombolysis group more days were spent without symptoms (232 *vs* 210 days in controls, p = 0·08), as illustrated by the larger area of class I after thrombolysis in fig 1. There were

Table 2 *Hospital admissions, hospital stay, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, and cardiac catheterisations in all patients, in patients with inferior and anterior infarction, and in the subgroup of patients with anterior infarction and extensive myocardial ischaemia admitted to the hospital within two hours of the onset of symptoms (see results)*

	All patients		*Inferior MI*		*Anterior MI*		*Anterior infarction $\sum ST \geqslant 1{\cdot}2\,mV$ admitted within 2 h*	
	C	*T*	*C*	*T*	*C*	*T*	*C*	*T*
Number of patients	264	269	148	139	116	130	50	45
Catheterisation + Sk		195		107		88		29
Catheterisation + Sk + PTCA		46		17		29		12
Elective catheterisation	205	199	120	99	85	100	35	38
Recurrent MI	14	36	9	26	5	10	2	4
Late PTCA	13	23	7	9	6	14	2	8
CABG	32	44	21	22	11	22	1	4
Other hospital admissions	74	75	41	39	33	36	18	16
Days in hospital (general ward)	4562	4500	2521	2310	2041	2190	791	689
Days in CCU	858	979	491	523	367	456	164	133
Days in surgical ICU	64	88	42	44	22	44	2	8

Sk, streptokinase; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting, CCU, coronary care unit; ICU, intensive care unit, $\sum$ ST: total ST segment elevation on the electrocardiogram made at admission to the trial.

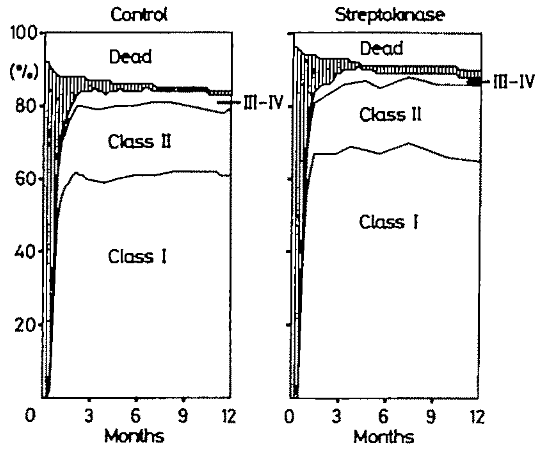

Fig 1 *Proportion of patients in each functional class during the first year after myocardial infarction. The shaded area represents admission to hospital. New York Heart Association classes III and IV are combined.*

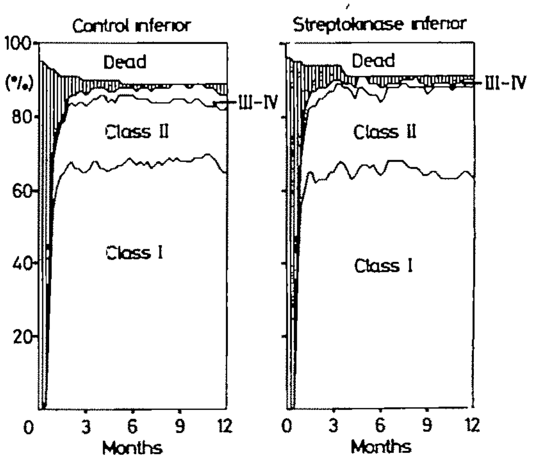

Fig 2 *Proportion of patients with inferior infarction in each functional class during the first year after myocardial infarction. See legend to fig 1.*

considerable differences in the efficacy of thrombolytic treatment between patients with anterior and those with inferior infarction. Mean survival at one year follow up after inferior infarction was 10 days longer in the thrombolysis group than in the control group (p = 0·4), although those on thrombolysis spent fewer days without symptoms (225 *vs* 232 days in controls, fig 2). In patients with anterior infarction differences in survival between the two treatment groups were more pronounced than those in the group with inferior infarction (fig 3). Mean survival was 35 days longer in the thrombolysis group (p = 0·02), and they had more days without symptoms (239 *vs* 183 days in controls, p = 0·002).

To take account of the opposite trends in mortality and morbidity, especially in patients with inferior infarction, quality adjusted survival was calculated by estimating the impairment of the quality of life by symptoms or hospital admission. Quality of life without symptoms (class I) was scored as 100%. Quality of life in class II was estimated as 90%, in class III or IV as 70%, and in hospital as 30%.[9] So quality adjusted mean survival for patients with inferior infarction was 307 days (out of 365 days) in the thrombolysis group and 300 days in the control group (table 3). In patients with anterior infarction quality adjusted survival was 38 days longer in the thrombolysis group than in the controls (p = 0·008).

The costs of medical treatment the first year after myocardial infarction were based on 1984 prices at the University Hospital Dijkzigt, Rotterdam. We included days spent in hospital (Dfl 600/day), days in a coronary care unit (Dfl 1500/day), days in a surgical intensive care unit (Dfl 2500/day), costs of acute cardiac catheterisation including thrombolytic treatment (Dfl 6200) or coronary angioplasty (Dfl 11 900), costs of elective catheterisation (Dfl 2600), elective coronary angioplasty (Dfl 8300), bypass surgery (Dfl

Table 3 *Mean number of days spent in the different functional classes or in hospital, quality adjustment for each situation (see results), and quality adjusted survival for all patients admitted to the trial and for patients with inferior or anterior infarction*

							Quality adjusted data						
	All patients		*Inferior MI*		*Anterior MI*		*Quality adjustment factor*	*All patients*		*Inferior MI*		*Anterior MI*	
	C	*T*	*C*	*T*	*C*	*T*		*C*	*T*	*C*	*T*	*C*	*T*
Class I	210	232	232	225	183	239	1·00	210	232	232	225	183	239
Class II	63	66	59	76	69	56	0·90	57	59	53	68	62	50
Class III-IV	14	9	10	8	19	10	0·70	10	7	7	6	13	7
In hospital	26	27	26	28	26	27	0·30	8	8	8	8	8	8
Mean survival (days)	313	334	327	337	297	332		285	306	300	307	266	304

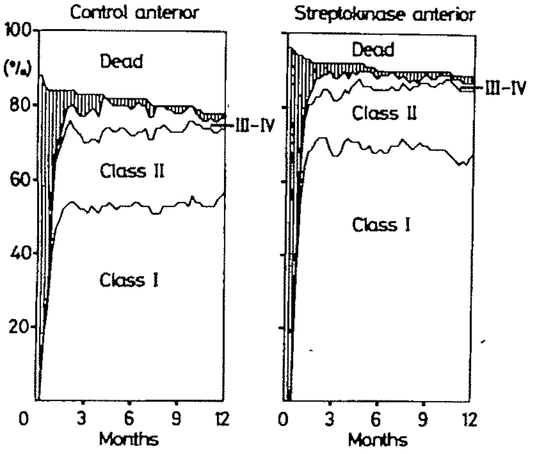

Fig 3 *Proportion of patients with anterior infarction in each functional class during the first year after myocardial infarction. See legend to fig 1.*

14 000), and medication prescribed during one year follow up (£1 ≃ Dfl 3·3). Total costs of medical treatment the first year after myocardial infarction averaged Dfl 21 000 for inferior infarction and Dfl 20 000 for anterior infarction in the control group, and Dfl 28 000 for inferior infarction and Dfl 29 000 for anterior infarction in patients allocated to thrombolytic treatment. The higher costs of patients allocated to thrombolytic treatment were mainly the result of acute catheterisation (table 4).

Life expectancy was calculated by the DEALE method.[10 11] A mortality rate of 6% per year was assumed for patients who were alive at the end of follow up. This assumption was based on long term prognosis after myocardial infarction seen in several large studies.[12-15] Thrombolytic treatment increased life expectancy (table 5), particularly in patients with anterior infarction (2·4 years). Additional costs per year of life gained were Dfl 3800 in patients with anterior infarction and Dfl 10 000 in inferior infarction.

Subgroup analysis showed the largest limitation of enzymatic infarct size and greatest reduction in three month mortality by thrombolytic treatment in patients with high total ST segment elevation ($\Sigma ST \geqslant 1{\cdot}2$ mV) admitted to the hospital within two hours of the onset of chest pain.[6] When this analysis was applied to life expectancy after myocardial infarction the effects of thrombolytic treatment were only apparent in patients with anterior infarction. Again, the greatest benefit was seen in patients with extensive myocardial ischaemia ($\Sigma ST \geqslant 1{\cdot}2$ mV), admitted to the hospital within two hours of the onset of symptoms. In this subgroup mean quality adjusted survival in the first year was 69 days longer in the thrombolysis group (310 *vs* 241 days in controls, $p = 0{\cdot}006$) and life expectancy was 3·6 years longer (table 5). Total costs of medical treatment in this subgroup were lower because there were fewer hospital admissions (table 2). Net costs per year of life gained by thrombolytic treatment were only Dfl 1900 in patients with large anterior infarctions who were admitted within two hours of the onset of symptoms.

Discussion

The randomised trial conducted by the Interuniversity Cardiology Institute of The Netherlands showed that early thrombolytic treatment can limit infarct size, improve left ventricular function, and reduce mortality. Improved survival after thrombolytic treatment was also reported by the Western Washington Trial[16] and to a lesser extent after intravenous streptokinase in the GISSI trial.[17] The present analysis indicates that this improved survival after thrombolytic treatment is accompanied by improved quality of life at an acceptably low cost.

Table 4 *Costs (Dfl)* of medical treatment in the first year after myocardial infarction.*

	All patients		*Inferior infarction*		*Anterior infarction*	
	C	*T*	*C*	*T*	*C*	*T*
Number of patients	264	269	148	139	116	130
Cost of:						
Catheterisation + Sk		1 209 000		663 000		546 000
Catheterisation + Sk + PTCA		547 000		202 000		345 000
Elective catheterisation	533 000	517 000	312 000	257 000	221 000	260 000
Late PTCA	208 000	191 000	58 000	75 000	50 000	116 000
Days in hospital (general ward)	2 738 000	2 700 000	1 513 000	1 386 000	1 225 000	1 314 000
Days in CCU	1 286 000	1 468 000	736 000	784 000	550 000	684 000
CABG + 2 days surgical ICU	608 000	836 000	399 000	418 000	209 000	418 000
Medication costs	198 000	204 000	106 000	102 000	92 000	102 000
Total	5 471 000	7 690 000	3 124 000	3 887 000	2 347 000	3 785 000
Average costs per patient	21 000	29 000	21 000	28 000	20 000	29 000

*Costs (Dfl) per patient for each item were respectively 6 200, 11 900, 2 600, 8 300, 600, 1 500, and 19 000 (£1 ≃ Dfl 3·3). Medication costs were based on standard dosages of prescribed cardiovascular drugs. See table 2 for abbreviations.

Table 5 *Calculation of costs (Dfl) per year of life gained in various groups of patients.*

	Mean life expectancy (yr)		*Costs*		*Costs per year of life gained*
	C	*T*	*C*	*T*	
All patients	15·3	16·8	21 000	29 000	5 300
Inferior infarction	16·3	17·0	21 000	28 000	10 000
Anterior infarction (all patients)	14·1	16·5	20 000	29 000	3 800
Anterior infarction (admission $\leqslant 2$ h and $\sum$ ST $\geqslant 1{\cdot}2$ mV)	12·7	16·3	18 000	25 000	1 900
Anterior infarction (admission 2–4 h or $\sum$ ST $< 1{\cdot}2$ mV)	15·1	16·6	22 000	32 000	6 700

See footnotes to tables 1 and 2.

The benefits of thrombolytic treatment were most clear cut in patients with anterior infarction—an observation that accords with the results of the GISSI trial.[17] The site of the infarct was based on electrocardiographic criteria, which were available shortly after hospital admission. Angiographic data were not used to determine the location of the infarction. Patients in the thrombolysis group in whom the infarct related obstruction was in the circumflex artery (as assessed by acute angiography) had electrocardiographic signs of anterior infarction in approximately 40% of the cases and of inferior infarction in 60%.

In this analysis all hospitals admissions were recorded and functional class was defined for each patient at regular intervals during one year follow up according to the method proposed by Olsson *et al.*[18] This enabled us to compare differences in mortality and morbidity between the two treatment groups. Although the assessment of impairment in the quality of life when angina pectoris or heart failure occur is dependent on the patient's opinion, the quality of life can be measured objectively by the patient's ability to carry on normal activity[9] as estimated by the Karnofsky Performance Status Scale. It is evident that in patients with anterior infarction thrombolytic treatment improved both life expectancy and quality of life, while the beneficial effects of thrombolytic treatment in inferior infarction remained small. These conclusions are independent of the method of quality adjustment, and remain unchanged when other quality adjustment factors are used. The total duration of hospital stay was the same in both treatment groups. However, admissions in the thrombolysis group were more often related to ischaemia (because of reinfarction and for additional revascularisation procedures such as coronary angioplasty or bypass surgery), whereas in the control group more admissions were the result of heart failure. This confirms that left ventricular function was more impaired in conventionally treated patients. The data shows that in both treatment groups most patients were free of symptoms during a one year follow up. The proportion of patients with symptoms was larger in the control group (33%) than in the thrombolysis group (22%) for patients with anterior infarction. Thus thrombolytic treatment improved survival and the quality of life in this group of patients. It is not clear why thrombolytic treatment was less effective in patients with inferior infarction. A possible explanation could be the higher reinfarction rate seen in these patients which abolishes the initially beneficial effects of thrombolytic treatment (table 1).

In the calculation of mean life expectancy a mortality rate of 6% per year was assumed for patients in both treatment groups. Sensitivity analysis indicated that the differences in mean life expectancy between the two treatment groups (table 5) persisted when a mortality rate of 5% or 7% was assumed for patients in both treatment groups. Long term prognosis depends on left ventricular function at discharge.[3] Since patients in the thrombolysis group had better left ventricular function than the control group,[3 5 6] the differences in mean life expectancy between the two treatment groups might even be underestimated, and the actual improvement of life expectancy by thrombolytic treatment might be greater than the data shown in table 5.

The true costs of thrombolytic treatment include the acute intervention as well as the higher incidence of reinfarction and additional revascularisation procedures. This is why we calculated total costs in the first year. We based the number of days in hospital (table 3) on a weekly assessment of functional state. This overestimated actual hospital stay which was 21 days in both treatment groups. Calculation of total costs was based on actual hospital stay, catheterisations, coronary angioplasty, and bypass surgery during follow up. Although thrombolytic treatment reduced the occurrence of ventricular fibrillation, cardiogenic shock, and heart failure,[1] the workload in the coronary care unit was not affected. The increased workload caused by the administration of thrombolytic treatment was balanced by the lower incidence of complications in the coronary care unit.[19] This is why we used the average costs for stay on the coronary care unit.

Total costs per patient during one year follow up appeared to be higher after thrombolytic treatment, mainly because of the costs of acute angiography and subsequent coronary angioplasty or bypass surgery. None the less, the cost benefit analysis shows that intracoronary thrombolytic treatment with streptokinase is cheaper than other established medical treatments. For example the cost of a one year increase in quality adjusted life expectancy after bypass surgery as calculated by Weinstein and Stason varied from Dfl 20 000 to Dfl 75 000[20] while the costs for treatment of moderate diastolic hypertension were Dfl 30 000 to Dfl 90 000 per year of life gained (£1 ≏ Dfl 3·3).[21] The cost benefit ratio of thrombolytic treatment is good because it requires only one intervention during hospital admission and has considerable beneficial effects, especially in patients with a larger anterior infarction. The treatment can thus be limited to a well defined and easily recognised group of patients, while hypertension treatment must be given to large numbers of patients for a long time in order to prevent or delay quite a small number of cardiovascular events.

A disadvantage of intracoronary thrombolytic treatment is the need for angiography during the acute stage. We included the costs of equipment and staff for a 24 hour angiography service in the analysis. We do not know how the cost benefit ratios of intracoronary thrombolysis and intravenous thrombolysis compare. Intravenous administration of streptokinase is initially less expensive, but also considerably less effective than intracoronary treatment in achieving patency, in salvage of myocardial function,[22] and in reducing mortality.[17] Careful analysis of follow up data of trials of intravenous streptokinase,[17,22] intravenous tissue plasminogen activator,[23–25] and intracoronary treatment (with or without immediate coronary angioplasty) should enable physicians and health authorities to decide upon the most cost effective method of thrombolytic treatment. Current data on intracoronary thrombolysis indicate that it is a cost effective treatment for patients with extensive anterior myocardial ischaemia[6,26] admitted early after the onset of symptoms of myocardial infarction.

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Plasminogen activator inhibitor activity and other fibrinolytic variables in patients with coronary artery disease

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SUMMARY Several fibrinolytic variables, including plasminogen activator inhibitor activity, were studied before and after exercise in 67 normolipidaemic patients with coronary artery disease and in 25 hyperlipidaemic patients with coronary artery disease. Before exercise plasminogen activator inhibitor activity was higher in the patient groups than in a group of 10 healthy volunteers. For those who were normolipidaemic plasminogen activator inhibitor activity was greater in patients with angina pectoris who had had a myocardial infarction. The concentration of antigenic tissue-type plasminogen activator was similar in all the patients with coronary artery disease and higher than in the control group. After the exercise test fibrinolytic capacity was lower in the patients with angina pectoris and a previous history of myocardial infarction. After exercise both the released immunological tissue-type plasminogen activator and fibrinolytic capacity were lower in the hyperlipidaemic patients than in the normolipidaemic patients. The concentration of plasminogen activator inhibitor was also higher in the hyperlipidaemic patients. Patients with hyperlipidaemia IV had the highest plasminogen activator inhibitor activity. The increase in plasminogen activator inhibitor activity found in the patients was partially inhibited by antiserum against plasminogen activator inhibitor-1 in vitro. The formation of a complex of about 115 000 daltons between plasminogen activator inhibitor and purified tissue-type plasminogen activator was detected by a zymographic fibrin technique.

These findings show that in patients with coronary artery disease fibrinolytic activity is impaired by an increase in plasminogen activator inhibitor. Impaired fibrinolysis may be related to the clinical evolution of coronary artery disease in these patients.

Fibrinolytic activity is impaired in many patients with coronary artery disease.[1-3] This impairment is detectable both in the resting state[4-6] and after physical exercise or venous occlusion.[7-9] It has been suggested that impaired fibrinolysis has a pathogenic role in coronary artery disease.[10] Impaired fibrinolysis could be caused by an increase in the activity of plasminogen activator inhibitor[11 12]; however, some groups have reported only a very occasional and transient increase in plasminogen activator inhibitor in patients with coronary artery disease.[13] In 1985 several groups reported increased concentrations of plasminogen activator inhibitor in patients with coronary artery disease and suggested that this increase may have a role in the pathogenesis of this disorder.[14-16]

The pathogenic role of plasminogen activator inhibitor in coronary artery disease was confirmed recently when a higher rate of reinfarction was found in patients with coronary artery disease with high concentrations of plasminogen activator inhibitor.[17 18] Others, however, reported no correlation between concentrations of plasminogen activator inhibitor and the severity of coronary disease.[15]

It has also been reported that hyperlipidaemia is usually associated with a decrease in fibrinolytic

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activity,[19 20] especially when it is caused by an increase in low density lipoproteins. Increased concentrations of high density lipoproteins were reported to have the opposite effect, that is they activated fibrinolysis.[21] These results were not, however, confirmed in another study.[22] It is clear, however, that patients with coronary artery disease who also have hyperlipidaemia generally have increased concentrations of plasminogen activator inhibitor, especially if the hyperlipidaemia is characterised by an increase in triglycerides,[15] whereas plasminogen activator inhibitor concentrations are usually normal in cases of hypercholesterolaemia.[16 23] Some workers found no correlation between triglyceride concentrations and plasminogen activator inhibitor in normal subjects.[24]

These data prompted an examination of possible correlations between the various clinical types of coronary artery disease and the concentration of plasminogen activator inhibitor and other fibrinolytic variables. We paid special attention to evaluating to what extent the presence or absence of a previous history of myocardial infarction was related to concentrations of plasminogen activator inhibitor in patients with angina.

Patients and methods

STUDY GROUPS

There were 67 men in the normolipidaemic group with coronary artery disease (group 1). None had hyperlipidaemia, hyperglycaemia, or severe hypertension. These patients were classified in three groups: (*a*) patients with angina pectoris without a previous history of myocardial infarction (n = 15); (*b*) patients with angina and a previous history of myocardial infarction (n = 14), and (*c*) patients who had had a myocardial infarction about three weeks before this study (n = 38).

Myocardial infarction or angina were diagnosed according to clinical, electrocardiographic, and enzymatic criteria.

We also studied 25 hyperlipidaemic men with coronary heart disease (group 2). These patients were classified into three groups as having hyperlipidaemia IIa, IIb, or IV. There were 10 healthy men in the control group. None had a history of angina or electrocardiographic evidence of ischaemic heart disease. Biochemical variables, particularly blood sugar and cholesterol concentrations, were normal.

All the subjects underwent a symptom limited bicycle ergometer test in a sitting position, starting with a workload of 30 W for three minutes. The workload was gradually increased by 25 W every three minutes. Each subject attained 85% of the individually expected maximal working capacity.

Table 1 shows characteristics of all the groups.

REAGENTS

The reagents for measuring functional protein C were obtained as described elsewhere.[25] Other reagents used were: chromogenic substrate S-2251 and human fibrinogen (Kabi Diagnostica, Stockholm), and bovine thrombin (Behringwerke AG, Marburg, West Germany). Human plasminogen was purified by lysine-sepharose chromatography,[26] followed by gel filtration on Sephadex G-150. Purified human single-chain tissue plasminogen activator from human melanoma cell culture (Biopool, Sweden) was used to measure the activity of plasminogen activator inhibitor. Human tissue-type plasminogen activator was also purified in our laboratory from Bowes-melanoma cell-culture conditioned medium, as described elsewhere.[27 28] It was purified without the addition of aprotinin and was obtained as double (75%) and single chain molecules (25%) and had a specific activity of 250 000 IU/mg

Table 1 *Characteristics of the study groups (mean (SD))*

	No	*Age*		*No of subjects with mild hypertension**	*No of subjects who were habitual smokers†*	*No of subjects of sedentary habits*	*Submaximal workload (W)*
		Mean	*Range*				
Group 1 (normolipidaemic).	67	54·6 (7·9)	(36–69)	22	39	17	115·6 (21·6)
Group A	15	55·9 (7·6)	(36–67)	6	6	3	109·4 (22·5)
Group B	14	56·7 (7·7)	(44–66)	4	3	2	119·0 (19·7)
Group C	38	52·5 (5·8)	(37–67)	12	30	12	116·8 (22·1)
Group 2 (hyperlipidaemic):	25	53·5 (8·8)	(37–69)	3	20	7	112·0 (23·0)
IIa	11	52·3 (8·2)	(42–69)	1	10	2	113·1 (29·7)
IIb	6	53·2 (13·5)	(37–68)	0	6	1	97·2 (11·4)
IV	8	56·2 (5·9)	(53–67)	2	4	4	124·9 (9·1)
Control group	10	49·3 (4·9)	(43–59)	0	8	3	153·3 (20·5)

*Mild hypertension: systolic blood pressure between 140–160 mm Hg and diastolic blood pressure up to 100 mm Hg.
†More than three cigarettes/day.

when measured by a clot lysis assay[28] with an international tissue-type plasminogen activator standard (National Institute for Biological Standards and Control reagent 83/517). Rabbit anti-bovine endothelial cell plasminogen activator inhibitor-1[29 30] and rabbit anti-plasminogen activator inhibitor-2 sera (Batch R3, approximate titre 150 μg/ml) were kindly donated by Dr D J Loskutoff (California, USA) and Dr E K O Kruithof (Lausanne, Switzerland) respectively. All other chemicals were of analytical grade.

METHODS

Venous blood samples at rest were obtained between 8.30 am and 9.30 am. Subjects remained in a sitting position for 10 to 15 minutes before venepuncture. Blood samples were obtained immediately after the exercise test. Blood was obtained and anticoagulated for the different tests as previously described.[31]

Whole serum cholesterol and triglycerides were measured by enzymatic methods. Protein C antigen was measured by an enzyme-linked immunosorbent assay method (Diagnostica Stago, France). The amidolytic and coagulant activities of protein C were assayed as previously described.[25] Antithrombin III was measured by an amidolytic method.[32]

Plasma euglobulin lysis time was measured by Buckell's method.[33] Fibrinolytic euglobulin activity was also measured on plasminogen-rich fibrin-agar plates as previously described.[14] Plasminogen and fast-acting antiplasmin activities were measured by chromogenic substrate methods.[34 35] Concentrations of fibrinogen/fibrin degradation products were measured by a haemagglutination inhibition method.[36] The activity of tissue-type plasminogen activator was measured by a functional method.[37] Plasminogen activator inhibitor activity was assayed as previously described.[37 38] One unit of inhibitor was defined as the amount that inhibits 1 IU of tissue-type plasminogen activator in 10 minutes (tissue-type plasminogen activator was calibrated against the international tissue-type plasminogen activator standard). Tissue-type plasminogen activator antigen was measured by an enzyme-linked immunoadsorbent assay method[39] (Biopool, Sweden), after acidification and neutralisation of plasma as previously described.[39]

The formation of tissue-type plasminogen activator/inhibitor complexes was studied by a zymographic fibrin overlayer technique[40] with a 7·5% polyacrylamide separating gel and a 4% polyacrylamide stacking gel. A volume (25 μl) of several dilutions of plasma was mixed with 2.5 μl of tissue-type plasminogen activator (25 U/ml). In another experiment 25 μl of a fixed dilution of plasma was mixed with several concentrations of tissue-type plasminogen activator. The mixtures were incubated for 10 minutes at 37°C. Then 25 μl of a buffer containing 0·125 mol/l TRIS-HCl, 4% sodium dodecyl sulphate, and 20% glycerol (pH 6·8) was added and the mixture was incubated for 15 minutes at 37°C. The samples were laid on the stacking gel and run at 25 mA for 3–4 hours at 4°C. The gels were washed for one hour in 2·5% Triton X-100 and for 20 minutes in deionised water. Fibrinolytically active bands were revealed by placing the gels on a plasminogen-rich fibrin-agarose gel and incubating them at 37°C in a humid environment for 18 hours. The molecular weight standards used were bovine serum albumin (68 000), phosphorylase (93 000), and β galactosidase (130 000).

The inactivation of plasminogen activator inhibitor activity by anti-plasminogen activator inhibitor-1 and anti-plasminogen activator inhibitor-2 was studied in three plasma samples from patients with ischaemic coronary disease and high plasminogen activator-inhibitory activity. Diluted plasma (50 μl, 1/4) was incubated with 5 μl of either diluted antibody (1/2) or diluted non-immune rabbit serum (1/2) or buffer for 15 minutes at 37°C. The residual inhibitory activity was assayed with tissue-type plasminogen activator (75% two chain tissue plasminogen activator) as described above.[37 38]

Mann-Whitney U and Student's *t* tests were used for statistical analysis.

Results

Concentrations of antithrombin III, protein C (functional and immunological), plasminogen, fibrinogen/fibrin degradation products, and α_2-antiplasmin at rest and after exercise were not significantly different in the clinical patient groups nor were there any differences between the control group and the patients.

Concentrations of immunological tissue-type plasminogen activator (table 2) were similar in groups A, B, and C, that is slightly higher than in the control group. In contrast, the concentration of immunological tissue-type plasminogen activator released after the exercise test was lower in patient groups A and B than in group C. The value in group C was similar to that of the control group. On the other hand, about 50% of the patients in group C had concentrations of released antigenic tissue-type plasminogen activator <3 ng/ml. This was higher than the concentration in the control group.

Fibrinolytic capacity (post-exercise fibrinolytic activity minus fibrinolytic activity at rest) was lower in patients with angina pectoris who had a history of myocardial infarction (group B) than in those with angina pectoris but no myocardial infarction (group

Table 2 *Fibrinolytic variables (mean (SD)) before (B) and after (A) exercise in normolipidaemic patients with coronary artery disease*

	Euglobulin lysis time (min) B	A	FC	*Lysis on fibrin plate (%)* B	A	FC	*Functional t-PA (U/ml)* B	A	t-PAC	*Antigen t-PA (ng/ml)* B	A	t-PAR	*PAI activity (U/ml)* B	A
Group A (n = 15)	248	178	69	113	213	99	0·34	1·31	0·98	12·2	15·5	3·2	2·67†	1·90*
	(60)	(70)	(49)	(97)	(172)	(104)	(0·35)	(1·9)	(1·60)	(3·1)	(5·6)	(4·9)	(2·24)	(2·06)
Group B (n = 14)	220	180	47*	99	157	58	0·29*	0·54*	0·32*	13·0	16·9	3·9	5·20†	4·4†
	(64)	(80)	(55)	(49)	(110)	(71)	(0·29)	(0·52)	(0·35)	(5·6)	(10·4)	(6·4)	(4·97)	(4·3)
Group C (n = 38)	263	154	108	84	211	110	0·27	1·25	0·93	13·2	18·8	5·6	3·7†	2·5*
	(87)	(91)	(91)	(43)	(138)	(147)	(0·43)	(1·70)	(1·41)	(6·3)	(10·0)	(4·0)	(4·2)	(3·4)
Control group (n = 10)	263	143	119	110	185	76	0·48	1·43	0·95	10·1	16·1	5·9	0·69	0·42
	(84)	(59)	(96)	(37)	(116)	(89)	(0·18)	(1·51)	(1·10)	(2·9)	(5·3)	(3·2)	(0·75)	(0·58)

*p < 0·05 compared with control group; †p < 0·02 compared with control group.
Group A, patients with angina pectoris without previous history of myocardial infarction, Group B, patients with angina pectoris and previous history of myocardial infarction; Group C, patients with myocardial infarction about 3 weeks before this study.
FC, fibrinolytic capacity (fibrinolytic activity after exercise minus fibrinolytic activity before exercise); t-PAC, tissue plasminogen activator capacity (T-Pa activity after exercise minus t-PA activity before exercise); t-PAR, t-PA release (antigen t-PA after exercise minus antigen t-PA before exercise); PAI, plasminogen activator inhibitor.

A) or those with recent myocardial infarction (group C) (table 2). This was found for both global assays (euglobulin lysis time and lysis on fibrin plate) and functional tissue-type plasminogen activator concentrations.

Plasminogen activator inhibitor activity at rest was higher in the three patient groups than in the control group. Moreover, 60% of the patients had plasminogen activator inhibitor values above 2 U/ml, a concentration that was never reached by the control subjects.

Patients with angina pectoris and myocardial infarction (group B) had higher plasminogen activator inhibitor activity than the other two groups. Furthermore, in four (28%) of the group B patients concentrations of plasminogen activator inhibitor were > 6 U/ml, a value that none of those in group A reached.

After the exercise test plasminogen activator inhibitor concentrations fell slightly in all the groups examined, but they continued to reflect the values at rest.

Released immunological tissue-type plasminogen activator and fibrinolytic capacity were lower and plasminogen activator inhibitor was higher in hyperlipidaemic patients with coronary artery disease (group 2) than in normolipidaemic patients with coronary artery disease (group 1) (table 3).

In patients with coronary artery disease plasminogen activator inhibitor activity was higher in those with types IIb and IV hyperlipidaemia than in those with type IIa hyperlipidaemia ($p < 0·05$) (table 4). The concentration of plasminogen activator inhibitor was lower in patients with type IIa hyperlipidaemia (approximately 2 U/ml) than in patients with the same pathology but without hyperlipidaemia (approximately 3·7 U/ml).

The residual plasminogen activator inhibitor activity of three plasma samples from coronary artery disease patients with high plasminogen activator inhibitor activity was measured after the addition of anti-plasminogen activator inhibitor-1 and anti-plasminogen activator inhibitor-2. The inhibitory capacity was reduced by anti-plasminogen activator

Table 3 *Fibrinolytic variables (mean (SD)) before (B) and after (A) exercise in various groups of patients with coronary artery disease*

	Euglobulin lysis time (min) B	A	FC	*Lysis on fibrin plate (%)* B	A	FC	*Functional t-PA (U/ml)* B	A	t-PAC	*Antigen t-PA (ng/ml)* B	A	t-PAR	*PAI activity (U/ml)* B	A
Group 1 (n = 61)	255	168	87	92·1	198	99§	0·28	1·11	0·81	12·8	17·6	4·6	3·73§	2·77‡
	(80)	(86)	(80)	(61·6)	(143)	(123)	(0·38)	(1·60)	(1·32)	(5·4)	(9·2)	(5·3)	(4·10)	(3·39)
Group 2 (n = 25)	251	187	64*	106	141	35§	0·24†	0·59*	0·37	12·8	16·8	3·8	5·70§	4·29‡
	(64)	(87)	(74)	(41)	(56)	(45)	(0·23)	(0·87)	(0·75)	(3·0)	(3·9)	(3·2)	(5·40)	(5·03)
Control group (n = 10)	263	143	119	110	185	76	0·48	1·43	0·95	10·1	16·1	5·9	0·69	0·42
	(84)	(59)	(96)	(37)	(116)	(89)	(0·18)	(1·51)	(1·10)	(2·9)	(5·3)	(3·2)	(0·75)	(0·58)

*p < 0·05 compared with control group, †p < 0·012 compared with control group; ‡p < 0·005 compared with control group, §p < 0·05 between group 1 and group 2. Group 1, normolipidaemic patients; Group 2, hyperlipidaemic patients
See footnote to table 2 for abbreviations.

Table 4 *Fibrinolytic variables (mean (SD)) before (B) and after (A) exercise in hyperlipidaemic patients with coronary artery disease*

	Euglobulin lysis time (min)			*Lysis on fibrin plate (%)*			*Functional t-PA (U/ml)*			*Antigen t-PA (ng/ml)*			*PAI activity (U/ml)*	
	B	*A*	*FC*	*B*	*A*	*FC*	*B*	*A*	*t-PAC*	*B*	*A*	*t-PAR*	*B*	*A*
Group IIa (n = 11)	246	203	43*	84	128	43	0·16†	0·52	0·40	13·1*	16·2	3·1	2·0	0·57
	(85·8)	(86)	(58)	(44)	(61)	(39)	(0·26)	(1·16)	(1·03)	(3·8)	(3·8)	(2·6)	(4·0)	(1·37)
Group IIb (n = 6)	260	174	87	145	167	22	0·26*	0·63	0·37	13·5*	17·3	3·8	7·5‡	6·75‡
	(36)	(90)	(95·4)	(21)	(79)	(67)	(0·19)	(0·39)	(0·34)	(3·1)	(1·9)	(1·6)	(4·6)	(4·12)
Group IV (n = 8)	249	175	73·7	110	143	33	0·37	0·69	0·32	11·9	17·2	4·8	9·4‡	7·55‡
	(53)	(95)	(76·4)	(27)	(28)	(41)	(0·14)	(0·59)	(0·49)	(1·4)	(5·6)	(5·0)	(4·48)	(5·73)
Controls group (n = 10)	263	143	119	110	185	76	0·48	1·43	0·95	10·1	16·1	5·9	0·69	0·42
	(84)	(59)	(96)	(37)	(116)	(89)	(0·18)	(1·51)	(1·10)	(2·9)	(5·3)	(3·2)	(0·75)	(0·58)

*p < 0·05 compared with control group; †p < 0·005 compared with control group; ‡p < 0·001 compared with control group.
See footnote to table 2 for abbreviations.

inhibitor-1 (66% of residual activity) but not by anti-plasminogen activator inhibitor-2 (91% of residual activity). Non-immune rabbit serum did not reduce the inhibitory capacity.

Use of a zymographic technique revealed the formation of a complex between the plasma plasminogen activator inhibitor and purified tissue-type plasminogen activator. The figure shows the formation of a complex between a fixed concentration of tissue-type plasminogen activator and plasma from a patient with coronary artery disease. Formation of the complex was reduced by dilution of the plasma (figure (a)). When we used a fixed dilution of patient plasma we found that as the tissue-type plasminogen activator concentration was increased, the complex also increased (figure (b)). This complex appeared to have a molecular weight of about 115 000 daltons.

Discussion

Our results accorded with those of other workers[14-16] who found that the concentration of basal antigenic tissue-type plasminogen activator at rest is slightly higher in patients with coronary artery disease than in controls. According to Hamsten *et al* this may be the result of a slow but continual release of tissue-type plasminogen activator from the vascular wall,[16] which could reduce the vascular deposits of tissue-type plasminogen activator in these patients and lead to a decreased release of tissue-type plasminogen activator after exercise. Our results seem to confirm this, because release of tissue-type plasminogen activator was lower after exercise in patients with a long history of angina pectoris (groups A and B) than patients with myocardial infarction (group C) in

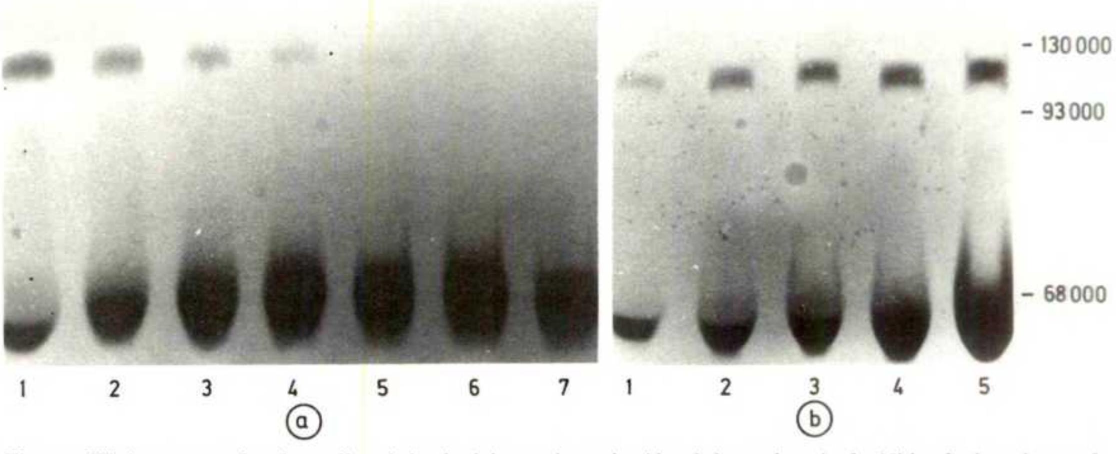

Figure *Fibrin-zymography after sodium dodecyl sulphate polyacrylamide gel electrophoresis of a 10′ incubation mixture of tissue-type plasminogen activator with coronary artery disease plasma. (a) Formation of a complex between purified tissue-type plasminogen activator (2·5 μl of 25 U/ml) and 25 μl of several dilutions of plasma (1 = 1/5; 2 = 1/10; 3 = 1/20; 4 = 1/40; 5 = 1/80; 6 = 1/160; 7 = buffer). (b) Formation of a complex between a fixed dilution (1/10) of plasma (25 μl) and 2·5 μl of tissue-type plasminogen activator (1 = 12·5 U/ml; 2 = 18·7 U/ml; 3 = 25 U/ml; 4 = 37·5 U/ml; 5 = 50 U/ml). A complex (115 000 daltons) formed between tissue-type plasminogen activator and the plasma plasminogen activator inhibitor.*

whom tissue-type plasminogen activator release resembled that seen in the control group.

We found that concentrations of plasminogen activator inhibitor activity were higher in patients with coronary artery disease than in controls. This finding accords with the results of earlier studies,[16 19 41] but we also found that patients with angina pectoris and previous myocardial infarction had higher concentrations of plasminogen activator inhibitor than patients with angina and no history of infarction. We believe that the higher concentration of plasminogen activator inhibitor may be related to the development of myocardial infarction in patients with angina pectoris. This suggestion accords with previous reports that reinfarction[17 18] and death[18] are more common in patients with coronary artery disease and high concentrations of plasminogen activator inhibitor.

The increase in plasminogen activator inhibitor may have been responsible for the reduced fibrinolytic capacity that we found in patients with angina pectoris and myocardial infarction (group B). There was no such reduction in patients with angina pectoris with no history of myocardial infarction (group A), even though both groups A and B had similar concentrations of released immunological tissue-type plasminogen activator.

These data support the hypothesis that plasminogen activator inhibitor has a pathogenic effect in patients with coronary artery disease and that this fibrinolytic inhibitor may impair fibrinolysis in these patients.

We found that hyperlipidaemic patients with coronary artery disease had reduced concentrations of released immunological tissue-type plasminogen activator after the exercise test, a higher concentration of plasminogen activator inhibitor and, as a consequence, a lower fibrinolytic capacity than normolipidaemic patients with coronary artery disease. These data accord with reports of increased plasminogen activator inhibitor in hyperlipidaemic individuals.[16] Like Hamsten *et al*[16] we also found that patients with coronary artery disease and hyperlipidaemia type IIa had lower concentrations of plasminogen activator inhibitor than patients with coronary artery disease who were normolipidaemic. In contrast, patients with coronary artery disease and type IIb or IV hyperlipidaemia had higher concentrations of plasminogen activator inhibitor.

The mechanism by which hypertriglyceridaemia could increase plasminogen activator inhibitor is not known[16] but there does seem to be an objective relation between these two variables. We do not know to what extent the possible alteration of the vascular wall in hypercholesterinaemic patients—which is normally more considerable than in hypertriglyceridaemic patients—is related to the decreased release of plasminogen activator inhibitor and tissue-type plasminogen activator.

Nevertheless, even in hypertriglyceridaemic patients with coronary artery disease who had plasminogen activator inhibitor concentrations that were higher than those in normolipidaemic patients with coronary artery disease, released plasminogen activator and the activity of circulating plasminogen activator inhibitor were lower when in addition to being hypertriglyceridaemic the patient was also hypercholesterinaemic (type IIb). The decreased release of tissue-type plasminogen activator that we found in coronary artery disease patients with type IIa hyperlipidaemia does not accord with the findings of Hamsten *et al*[16] who found that tissue-type plasminogen activator release after venous occlusion was adequate. This may be because they studied young patients, who were less likely to have the atherosclerotic alterations than our patients.

In conclusion, our results suggest that the greater increase in plasminogen activator inhibitor in patients with angina pectoris and previous myocardial infarction may be associated with this acute event. It may be that concentrations of plasminogen activator inhibitor in coronary artery disease patients are of prognostic value.

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Clinical implications of pulmonary regurgitation in healthy individuals: detection by cross sectional pulsed Doppler echocardiography

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SUMMARY Pulsed Doppler echocardiography in healthy individuals often shows a disturbance of diastolic flow in the right ventricular outflow tract just below the pulmonary valve that suggests regurgitation. This disturbance of diastolic flow was studied in 50 healthy individuals and 40 patients with cardiopulmonary disease, some of whom had a pulmonary regurgitant murmur. Diastolic flow was disturbed in 39 of the 50 healthy individuals. In 32, cross sectional echocardiography gave a satisfactory image of the pulmonary valve. The characteristic Doppler signals usually lasted throughout diastole, were directed toward the right ventricular cavity, and gradually waned towards end diastole; they formed a spindle shaped area of abnormal signals that extended to within 10 mm of the coaptation of the pulmonary valve towards the right ventricular cavity and the pressure difference estimated from the signals by the modified Bernoulli equation seemed to be proportional to the normal retrograde transpulmonary pressure difference. In all 40 patients with cardiopulmonary disease, signals indicating pulmonary regurgitation were found whether or not a regurgitant murmur was present. When it was present, however, the spindle was longer than 20 mm and in patients with pulmonary hypertension the velocity of abnormal diastolic flow was higher than in healthy individuals. The Doppler signals registering disturbed flow in the healthy individuals resembled the signals caused by pulmonary regurgitation in the patients in terms of location, orientation, and configuration.

These results show that healthy individuals usually have trivial pulmonary regurgitation. In practice the distance that the flow disturbance extends from the valve and estimated pressure difference across the valve are probably the most important variables for assessing the clinical significance of pulmonary valve regurgitation.

Doppler echocardiography is a sensitive and specific technique for detecting valve regurgitation.[1-4] Even in healthy subjects, unusual Doppler signals are often seen just beneath the pulmonary valve in the right ventricular outflow tract during diastole; these are apparently signals from pulmonary regurgitation. We have examined a series of healthy individuals for these signals to find out whether they indicate true regurgitation and are clinically significant.

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Patients and methods

We examined 50 healthy individuals aged 23 to 59 years (mean 35 years) and 40 patients with cardiopulmonary disease aged 19 to 68 years (mean 40 years). The 50 healthy individuals had no history of cardiopulmonary disease and no abnormality on physical examination and cross sectional echocardiography. The 40 patients with cardiopulmonary disease all had echocardiograms that clearly showed the right ventricular outflow tract and pulmonary valve. Nineteen had acquired valve disease, 14 had congenital heart disease, two had cardiomyopathy, two had idiopathic dilatation of the pulmonary artery, two had pulmonary embolism, and one had primary pulmonary hypertension. Phonocardiography performed simultaneously with the Doppler examination showed a pulmonary regurgitant murmur in 12 of the 40 patients. The remaining 28 patients did not have a diastolic murmur.

METHODS

Equipment

We used two commercially available cross sectional pulsed Doppler echocardiograms, a Toshiba SSH-11A/SDS-10A and a SSH-40A/SDS-21A. The transducer frequency was 2·4 MHz and the pulse repetition rate was 6000 bursts/s (1 kHz of Doppler frequency is equivalent to 31 cm/s flow velocity). The sample volume size was 4 × 4 mm in width and 2 mm in depth. A 400 Hz high-pass filter was used to eliminate artefacts caused by cardiac wall motion. The frequency analysis was carried out by fast Fourier transformation. Doppler beam direction and the site of sample volume were displayed on the cross sectional echo image of the heart. Analysed Doppler signals were displayed as a sound spectrogram with the electrocardiogram, phonocardiogram, and M mode echocardiogram on a strip chart recording paper (paper speed 50 mm/s). Flow components towards and away from the transducer were displayed as flow signals above and below the baseline, respectively.

Ten of the 50 healthy individuals were also examined by colour-coded real time cross sectional Doppler flow imaging to confirm the finding obtained by the conventional method.[5] In this technique, Doppler flow signals were processed by the high-speed autocorrelation technique, so that flow direction, mean velocity, and degree of flow dispersion were simultaneously displayed on the same site in the cross sectional echo image of the heart with colour codes in real time. A red code indicated the flow component toward the transducer and blue showed flow away from the transducer. The colour intensity expressed the magnitude of flow velocity and green was added to the red or blue to show the degree of flow dispersion.

SEARCHING TECHNIQUE

The sagittal cross sectional view of the right ventricular outflow tract including the pulmonary valve was obtained through the third or fourth intercostal space. Then the transducer was gradually tilted to obtain sagittal cross sectional views over the whole right ventricular outflow tract. We analysed the flow pattern on each cross sectional plane. The area just beneath the pulmonary valve was examined for jets in diastole. In the healthy individuals Doppler signals indicating jet flow were detected near the pulmonary valve in the right ventricular outflow tract during diastole. These signals had a wide velocity spectrum with flow away from the pulmonary valve and lasted more than 200 ms in diastole (fig 1a). In early diastole signals lasting < 200 ms were not considered because in that phase it is difficult to exclude the influence of the valve and wall motion on the record.

When Doppler signals indicating disturbed diastolic flow were detected we recorded the cross sectional cut that showed the full extent of the signal. This view was frozen in mid diastole and the distribution of the signal was mapped by gradually changing the beam direction as described elsewhere.[6 7]

Quality of the echocardiographic image of the pulmonary valve

The quality of the echocardiographic image of the pulmonary valve was graded as: good (visualisation of two or three cusps of the pulmonary valve); poor (only one cusp visualised); none (none of the cusps was clearly visualised).

Results

FREQUENCY OF ABNORMAL DOPPLER SIGNALS IN HEALTHY INDIVIDUALS

Doppler signals indicating a jet-like disturbance of flow were detected in 39 (78%) of the 50 healthy individuals examined. The quality of the echo image of the pulmonary valve was good in 32 and poor in 11. In the remaining seven, the pulmonary valve was not visualised. Doppler signals showing a jet-like flow disturbance were detected in all 32 healthy individuals with the good image of the pulmonary valve, in seven of the 11 subjects with the poor image, and in none of the seven subjects whose valves were not visualised (table). Thus the disturbance of diastolic flow was invariably detected when the quality of the echo image of the pulmonary valve was good.

CHARACTERISTIC FEATURES OF SIGNALS SHOWING JET-LIKE FLOW DISTURBANCE IN DIASTOLE

In diastole disturbed Doppler signals were found in a small spindle-shaped region extending from the coaptation site of the pulmonary valve into the right

Table *Frequency of disturbed Doppler signals showing a jet-like flow in the subpulmonary region in relation to the quality of the echocardiographic image of the pulmonary valve*

Image quality	*Detected*	*Not detected*	*Total*
Good	32	0	32
Poor	7	4	11
None	0	7	7

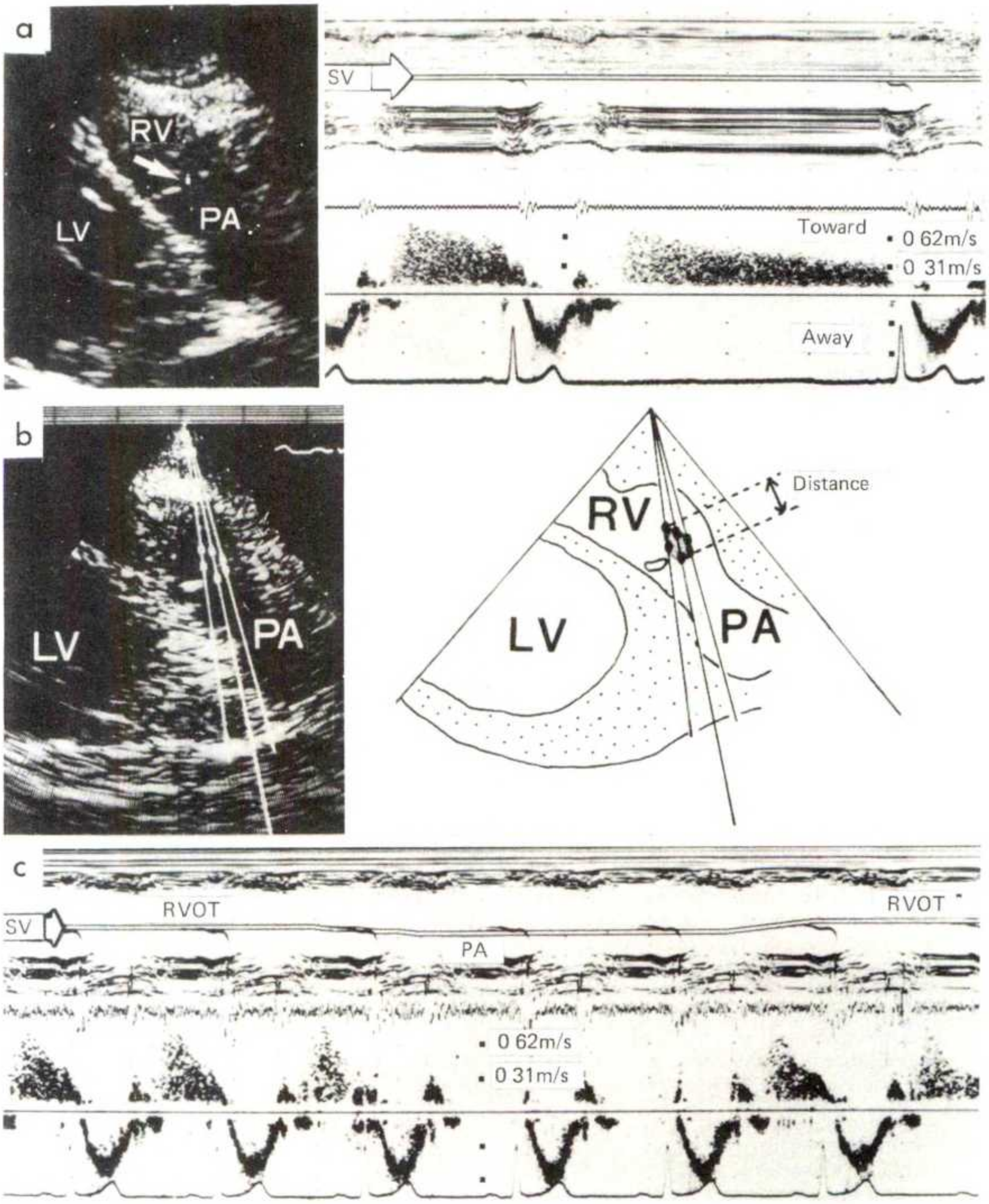

Fig 1 *Doppler signals showing jet-like disturbance of flow just beneath the pulmonary valve (a) Left: Parasternal sagittal view of the basal part of the heart. The broken line indicates the direction of the Doppler beam, and the sample volume is represented by a large dot (arrow). The sample volume lay just beneath the coaptation site of the pulmonary valve in the right ventricular outflow tract. Right: Doppler signals recorded in diastole at the sample volume indicated in (a) left. The signals show a wide-band velocity spectrum away from the pulmonary valve. The flow velocity gradually decreased toward end diastole from the maximum of about 0·7 m/s in early diastole. (b) Left: parasternal sagittal view. The subpulmonary area was searched for the signals of flow disturbance in diastole (see the change in the beam direction and the site of sample volume on each beam). The positions of the thick white dots show where such signals were detected. (b) Right: diagrammatic representation of (b) left. The maximum distance reached by the signals of flow disturbance is shown. (c) M mode echocardiogram of the pulmonary area and the frequency spectrogram of the signals of flow disturbance obtained there. The location of the sample volume in diastole was gradually shifted from near the pulmonary valve in the right ventricular outflow tract to the pulmonary trunk and then back again. Signals showing disturbed flow in diastole appeared only near the pulmonary valve and never in the pulmonary trunk. RV, right ventricle; LV, left ventricle; PA, pulmonary artery; RVOT, right ventricular outflow tract; SV, sample volume.*

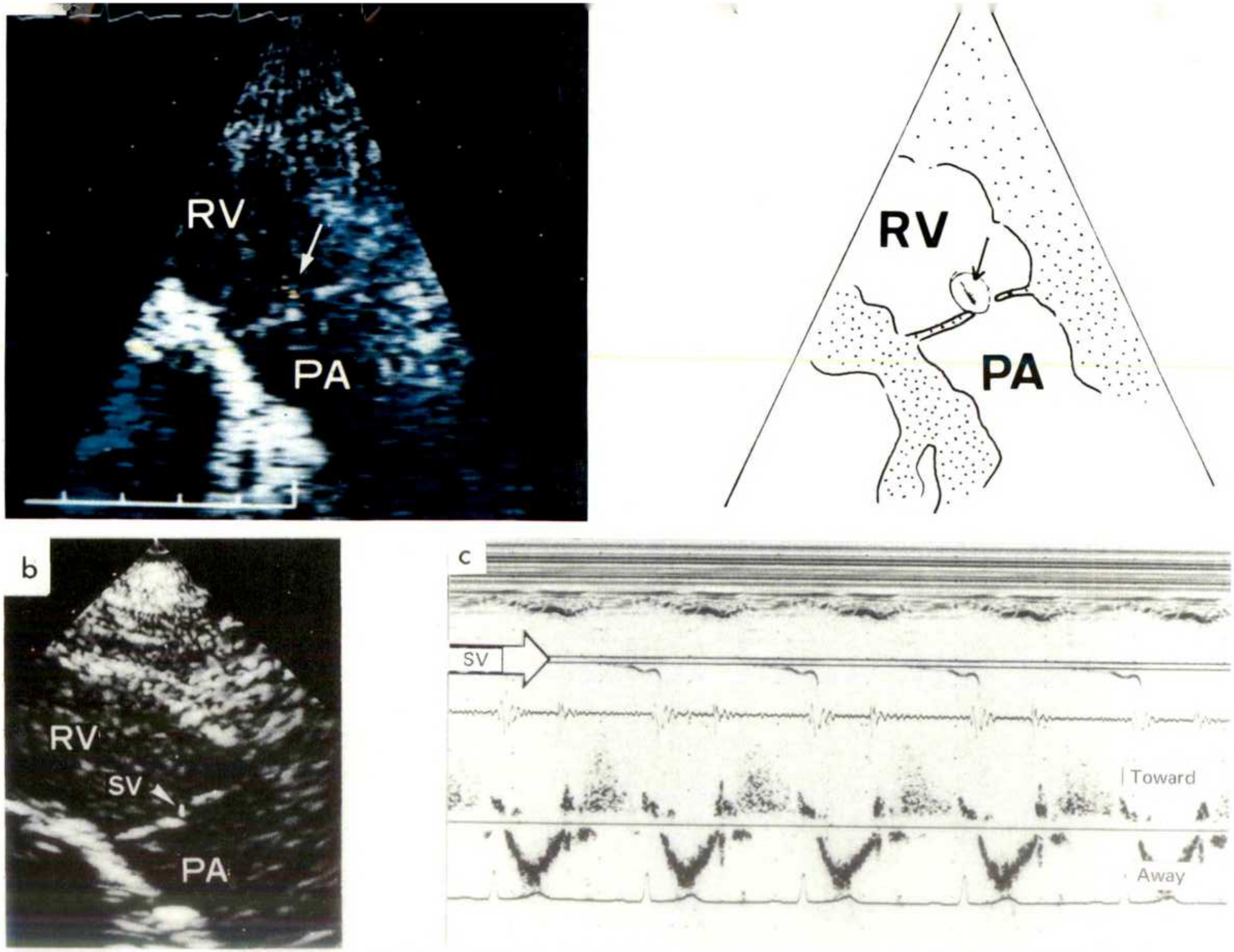

Fig 2 *Colour flow image of the unusual Doppler signals in a healthy 36 year old man. (a) a small reddish jet spurted from the coaptation site of the pulmonary valve into the right ventricular cavity. (b) The sample volume for Doppler signals was very close to the coaptation site of the pulmonary valve in the right ventricular outflow tract (white arrow). (c) Doppler frequency spectrogram of the small jet. The M mode echocardiogram shows that the sample volume was very close to the pulmonary valve during diastole. See fig 1 for abbreviations.*

ventricular outflow tract, but they were never found in the pulmonary trunk (fig 1). They were audible as high pitched decrescendoes that resembled signals caused by aortic and pulmonary regurgitation. Although none of the healthy subjects had a murmur indicating pulmonary regurgitation, the unusual Doppler signals were almost indistinguishable from the pulmonary regurgitant signals obtained from patients with pulmonary regurgitant murmurs in terms of flow direction, distribution, and other properties.

The maximal distances to which the signals of the flow disturbance extended from the pulmonary orifice were $\leqslant 10$ mm except in one case in which the distance was 12 mm (fig 1b). The velocity of these Doppler signals was fastest in early diastole and then gradually declined towards end diastole (fig 1a). The maximal velocity of the diastolic disturbed flow in one pulse period ranged from 0·7 to 1·5 m/s in healthy subjects. According to the modified Bernoulli equation, this velocity corresponds to pressure difference of about 2 to 9 mm Hg.

The real time cross sectional Doppler flow imaging technique was applied to ten of the 39 healthy subjects in whom Doppler signals, showing a jet-like flow disturbance, were detected by the conventional method. It invariably showed a trivial, but definite, jet flow spurting from the coaptation site of the pulmonary valve into the right ventricular cavity (fig 2). The characteristics of these Doppler signals were identical with those seen in the patients with pulmonary regurgitation.

DISTINGUISHING THE JET-LIKE DISTURBED FLOW FROM OTHER FLOWS IN THE RIGHT VENTRICULAR OUTFLOW TRACT

Flow velocity measured around the jet-like disturbed flow fell off abruptly. No other rapid flows were detected near the jet-like flow in the right ventricular outflow tract during diastole. Careful examination, however, showed two kinds of slow stream near the pulmonary valve in the right ventricular outflow tract in diastole (fig 3). One was a flow toward the pulmonary valve in the anterior and central parts of the outflow tract, and the other was a flow away from the pulmonary valve, on the septal side. The flow towards the valve seemed to be the tricuspid inflow reaching the outflow tract. Reversal of this flow just beneath the pulmonary valve may give rise to the flow away from the valve. The jet-like disturbed flow was quite different from these flows in velocity and topography.

SIMILARITY BETWEEN JET-LIKE FLOW DISTURBANCE SIGNALS IN HEALTHY SUBJECTS AND REGURGITANT SIGNALS IN PATIENTS WITH PULMONARY REGURGITATION

Twelve of the 40 patients with cardiopulmonary disease had a pulmonary regurgitant murmur. This produced jet-like signals from the coaptation site into the right ventricular cavity. Eight of these 12 patients had pulmonary hypertension. The frequency spectrogram showed multiple aliasing, indicating that the velocity was higher than the upper limit of the measurable range (that is, 2 m/s) and the upper limit of the healthy subjects (1·5 m/s). In the remaining four patients (two with idiopathic dilatation of the pulmonary artery and two with tetralogy of Fallot after operation) the flow velocity was within the normal range. The distance reached by the regurgitant flow was 20 mm or further in all 12 patients (fig 4).

In the 28 patients without a pulmonary regurgitant murmur, we detected jet-like Doppler signals from the coaptation site of the pulmonary valve. Although these signals resembled the pulmonary regurgitant signals in configuration and orientation, they were generally shorter (>20 mm in two patients, between 10 and 20 mm in 16, and <10 mm in 10). Although in an earlier study we reported that these signals indicate silent pulmonary regurgitation,[4] in the last 10 patients the signals (<10 mm) were identical to those of the jet-like flow disturbance that we found in healthy individuals.

Discussion

DO THE DOPPLER SIGNALS SHOWING A JET-LIKE DISTURBANCE OF FLOW IN THE RIGHT VENTRICULAR OUTFLOW TRACT OF HEALTHY SUBJECTS INDICATE TRUE PULMONARY REGURGITATION?

With the pulsed Doppler technique, valve regurgitation is diagnosed when high-frequency Doppler signals with wide-band spectrum are detected extending backward from the malfunctioning valve.[7-9] We found Doppler signals, showing a jet-like disturbance of flow in healthy subjects, with the following features: (1) a long duration in diastole; (2) spurting from the coaptation site of the pulmonary valve, with velocity toward the right ventricular cavity; (3) spindle-like configuration; (4) and a flow velocity that was nearly the same as the transpulmonary pressure difference. The falling off in velocity towards end diastole also corresponds to the time course of the transpulmonary pressure gradient in diastole. Apart from the distance reached by the jet all features resemble the signals recorded in pulmonary regurgitation. In those patients with cardiopulmonary

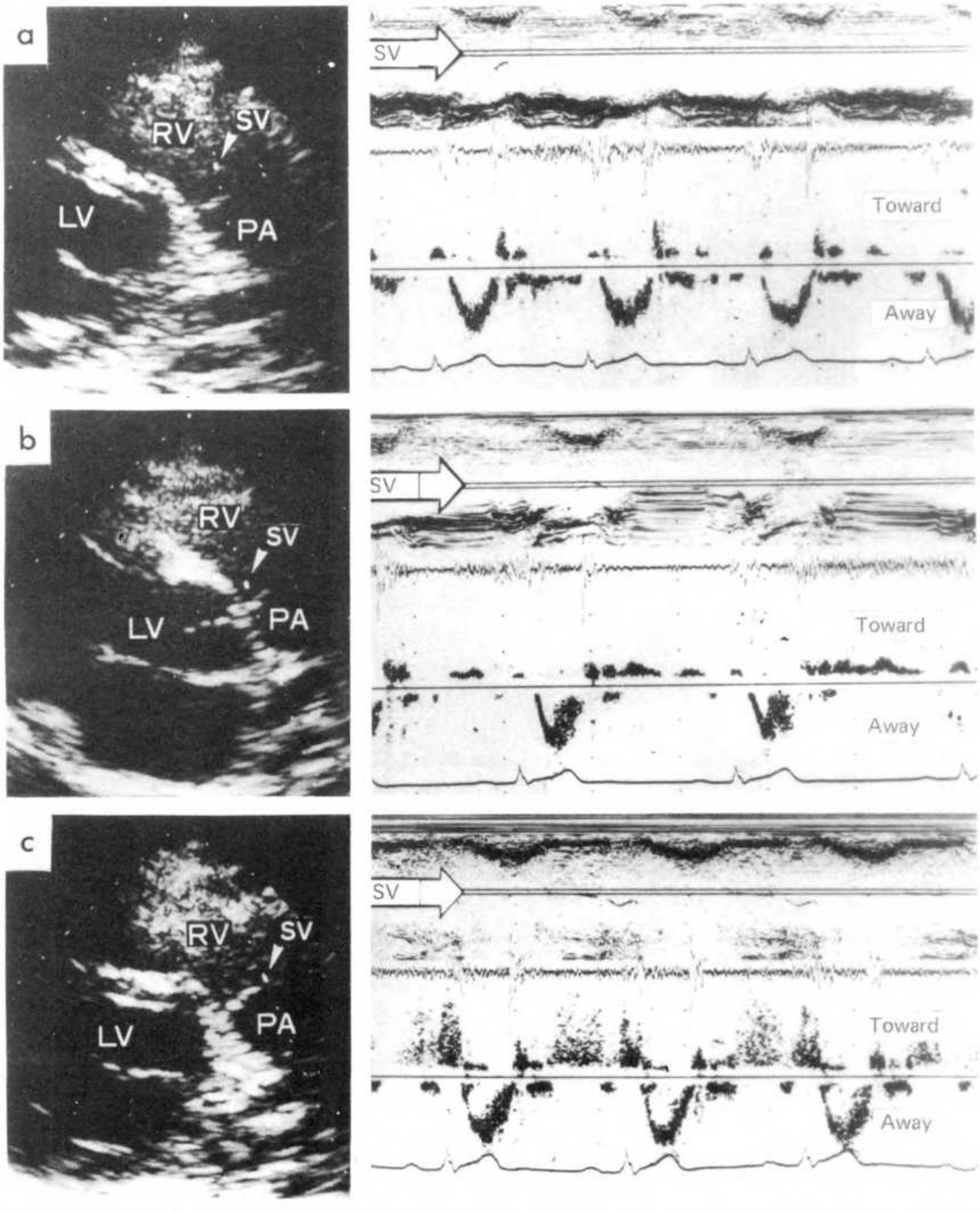

Fig 3 *Doppler signals surrounding the jet-like disturbance of flow in the subpulmonary region in a healthy 28 year old man. (a) Left: sample volume for Doppler signals lies near the pulmonary valve in the central part of the right ventricular outflow tract (arrow). (a) Right: slow flow towards the pulmonary valve was recorded by the sample volume (a, left) in diastole. (b) Slow flow away from the pulmonary valve was recorded near the interventricular septum. (c) There were Doppler signals with a wide-band frequency spectrum in a localised area close to the coaptation site of the pulmonary valve. These were distinct from the flows seen in a and b. See fig 1 for abbreviations.*

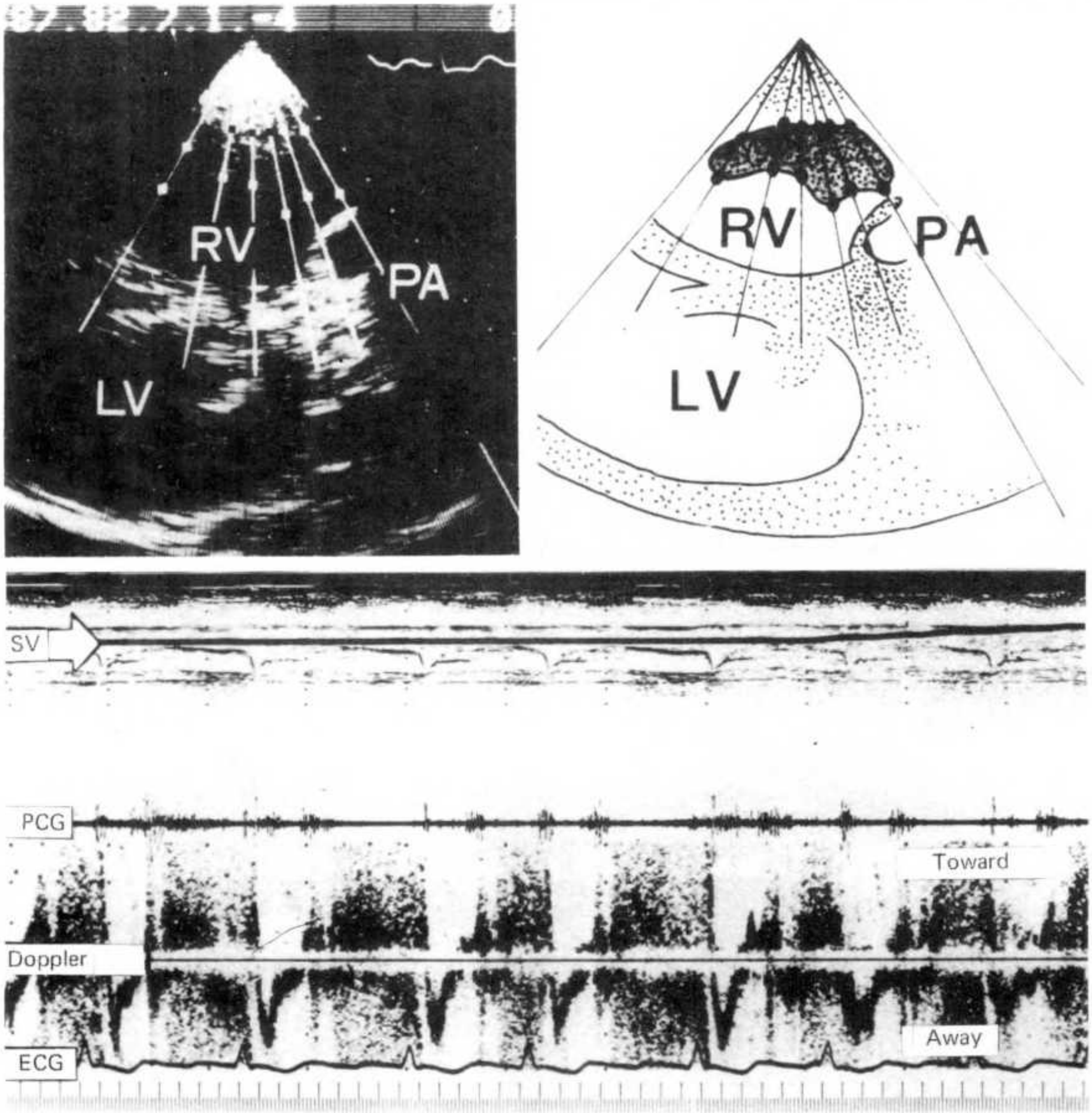

Fig 4 *Doppler signals in a 40 year old woman with Eisenmenger's syndrome and a pulmonary regurgitant murmur. Parasternal sagittal view of the basal part of the heart and its diagram (above). The region where pulmonary regurgitant Doppler signals were detected is shown by thick white dots. The frequency spectrogram of the pulmonary regurgitant Doppler signals (below) shows aliasing, indicating that the regurgitant jet had a high velocity caused by pulmonary hypertension. See fig 1 for abbreviations.*

disease who might have silent pulmonary regurgitation, the length of the jet was less than that in the patients with documented pulmonary regurgitation and more than that in the healthy subjects. This continuous spectrum of Doppler signals from confirmed pulmonary regurgitation to normality suggests that when a jet-like flow disturbance is found in healthy subjects it should be interpreted as trivial pulmonary regurgitation.

But there may be explanations other than regurgitation through the pulmonary valve for this flow disturbance in healthy subjects: (*a*) the pulmonary ejection flow which reverses just above the pulmonary valve in the pulmonary trunk may be mistaken for a pulmonary regurgitant flow; (*b*) the closing movements of the pulmonary cusps can cause flow away from the pulmonary valve that mimicks pulmonary regurgitation; (*c*) the tricuspid inflow stream reaching the right ventricular outflow tract could reverse just beneath the pulmonary valve to form the flow which is confused with a pulmonary regurgitant flow. The first possibility is ruled out because Doppler signals showing a jet-like flow disturbance are detected only just beneath the pulmonary valve and never in the pulmonary trunk. The second possibility is ruled out because the Doppler signals persist throughout diastole. It is true that the tricuspid inflow reached the right ventricular outflow tract and became reversed just beneath the pulmonary valve. However, it produced Doppler signals that were conspicuously different from the jet flow that we detected.

Yock *et al* detected flow in the opposite direction to right ventricular ejection during diastole in 40% of healthy adults by the continuous wave Doppler technique.[10] They thought that the Doppler signal represented pulmonary regurgitant flow because the flow signal was enhanced by intravenous injection of saline and because the application of the modified Bernoulli equation to this flow signal predicted a pressure difference of <10 mm Hg, which is equivalent to the retrograde transpulmonary difference in diastole. The continuous wave Doppler technique does not distinguish the abnormal flow signals from the surrounding flow signals. In the present study, the pulsed Doppler technique clearly demonstrated that the Doppler signals from jet-like flow disturbance were confined to the region extending from the coaptation site of the pulmonary valve into the right ventricular cavity and were distinct from the other surrounding flows.

Because this kind of flow was invariably detected in the healthy subjects in whom the coaptation site of the pulmonary valves was clearly imaged on the cross sectional echocardiogram, we assume that it is normal for healthy subjects to have trivial regurgitation through the pulmonary valve.

CAUSES OF REGURGITATION THROUGH THE NORMAL PULMONARY VALVE

The semilunar valves are designed to eject the blood effectively and to prevent regurgitation.[11 12] So why should trivial regurgitation through the pulmonary valve be a normal finding in healthy individuals? Certainly the pulmonary valve is less tight than that of the aortic valve[13 14] (that is, it has a less tight fibrous

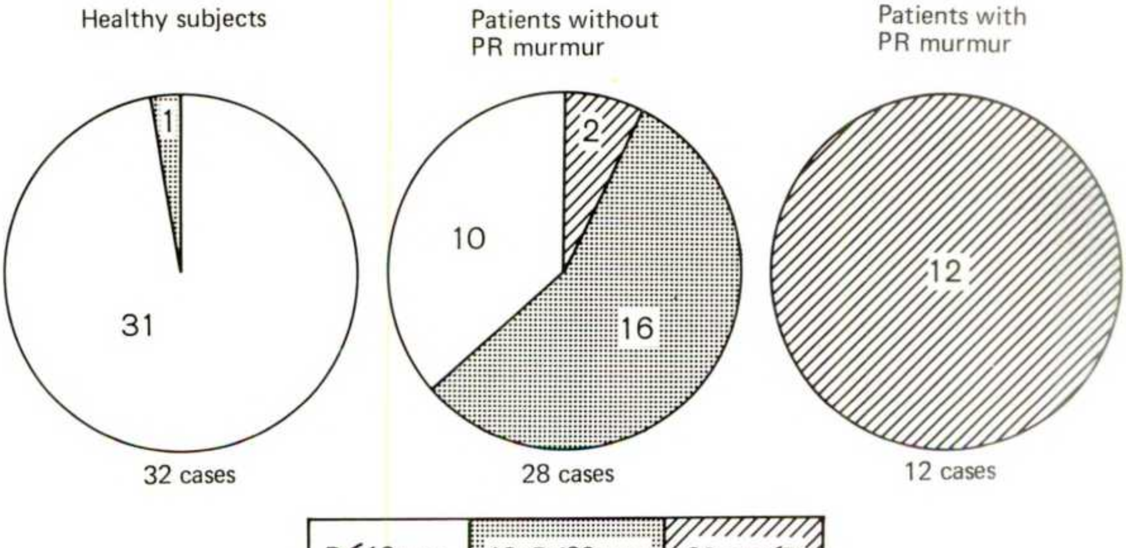

Fig 5 *The maximum distances reached by the diastolic disturbed flow signal in healthy subjects and in patients with cardiopulmonary disease. The maximum distance was measured in 32 healthy subjects in whom the pulmonary valve was well visualised. The distance was $\leqslant 10$ mm in 31 of them. In all the patients with a pulmonary regurgitant murmur the distance was $\geqslant 20$ mm. In the group of patients with no pulmonary regurgitant murmur the maximum distance lay between that of the healthy group and the group with a murmur. D, maximum distance of regurgitant signal; PR, pulmonary regurgitant.*

ring, thinner cusps, a more hypoplastic Alantius nodule, and shallower sinuses). Furthermore, the retrograde pressure gradient through the pulmonary valve in diastole may not be enough to close the valve as tightly as the aortic valve.

This tendency to regurgitation may mitigate against lung congestion by moderating the pressure rise in the pulmonary capillaries by reducing the excessive preload to the left side of the heart.

CLINICAL IMPLICATION

Patients with rheumatic heart disease often have Doppler signals typical of pulmonary regurgitation.[3 4] In some, these were thought to indicate silent pulmonary regurgitation.[4] The present study, however, shows that such signals are not always abnormal, because healthy individuals commonly have trivial pulmonary regurgitation. Therefore, whenever pulmonary regurgitant signals are detected, their clinical significance should be assessed before they are attributed to cardiopulmonary diseases.

The signals have two important properties. The first is velocity, which may reflect a retrograde transpulmonary pressure difference during diastole. In healthy individuals the transpulmonary pressure gradient is small in diastole. Maximal velocity was $<1{\cdot}5$ m/s of all our healthy individuals, and this is consistent with the normal retrograde transpulmonary pressure difference expected of $<4 \times 1{\cdot}5^2 = 9$ mm Hg (modified Bernoulli equation). In those with pulmonary hypertension, the maximal velocity of the pulmonary regurgitation was well above the physiological range. In patients with pulmonary regurgitant murmur, but not pulmonary hypertension, the regurgitant flow velocity was the same as that in healthy subjects. This finding is discussed below.

The second important property of the pulmonary regurgitant signal is the maximum distance travelled by the signals from the pulmonary orifice into the right ventricle. The maximum distance travelled by regurgitant signals from the regurgitant orifice correlated roughly with the degree of regurgitation.[6 7] While the distance was usually $\leqslant 10$ mm in the healthy individuals, it was $\geqslant 20$ mm in all 12 patients with pulmonary regurgitant murmurs in whom regurgitation was an expected finding. Distances of $\leqslant 10$ mm may be accepted as being within the physiological range, those >10 mm to 20 mm as borderline, and those $\geqslant 20$ mm as indicating clinically important regurgitation (fig 5).

The figure of 10 mm is not an absolute marker for pulmonary regurgitation. This is because it is difficult to measure accurately the precise distance reached by the pulmonary regurgitant signal because the right ventricular outflow tract is anatomically complex. There are still problems with resolution and gain with current equipment. Nevertheless, these difficulties should not obscure the importance of measuring this distance which, together with the velocity, is the major determinant for assessing the clinical significance of signals indicating pulmonary regurgitation.

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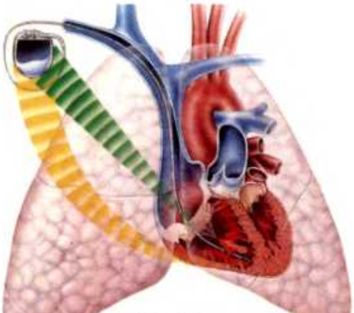

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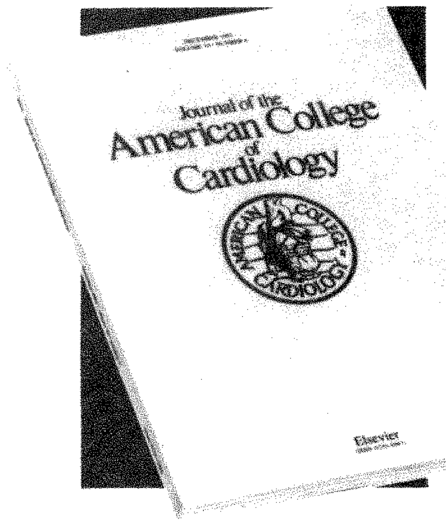
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Limitations in assessing the severity of aortic stenosis by Doppler gradients

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SUMMARY Continuous wave Doppler echocardiography was performed before cardiac catheterisation in 69 consecutive patients with suspected aortic stenosis. Agreement between the maximum and the mean Doppler gradients and catheterisation gradients was good. Doppler echocardiography, however, systematically underestimated the maximum and mean gradients, particularly in the high range. Stepwise regression analysis of the small pressure difference between the two methods showed that it could not be explained by age, sex, stroke volume, differences in heart rate, ejection fraction, the presence of coronary artery disease, or severity of aortic regurgitation. There was a negative curvilinear correlation between the maximum and mean Doppler gradients and the aortic valve areas that were measured at catheterisation in patients with pure aortic stenosis. The degree of correlation decreased when patients with concomitant aortic regurgitation were included. The scatter of gradients above and below the correlation line was large and this was caused by low and high transvalvar flow.

These results show that the usefulness of Doppler gradients for judging the severity of aortic stenosis, both in relation to immediate diagnosis and follow up, is severely limited if transvalvar flow is not taken into account.

Several recent studies have shown the usefulness of Doppler echocardiography in assessing the systolic transvalvar pressure gradient in aortic stenosis.[1-3] In these studies and in others[4-6] variables were studied that might cause differences between calculated Doppler gradients and those measured at cardiac catheterisation, such as the age of the patient, the presence of aortic regurgitation, atrial fibrillation, low cardiac output, left ventricular function, associated coronary artery disease, and the experience of the operator with the Doppler technique. But such variables were only evaluated by subgroup analysis.

The decision on whether a patient should undergo aortic valve replacement is primarily based on the assessment of the aortic valve area, which is regarded as the most exact laboratory value.[7] Although the systolic pressure gradient is an important determinant of the area, as reflected in the Gorlin formula,[8] the calculated area is also influenced by the transvalvar flow.

The object of our study was to evaluate the usefulness of transvalvar gradients measured by Doppler echocardiography in predicting the severity of aortic stenosis (determined as the aortic valve area at catheterisation) in consecutive patients. To overcome some of the previous limitations of subgroup analysis we used stepwise regression analysis to assess the influence of physiological variables on the differences between the Doppler and catheterisation gradients.

Patients and methods

PATIENTS

Sixty nine consecutive patients (42 men) referred for cardiac catheterisation with suspected aortic stenosis, alone or in combination with other valve lesions, were evaluated from January 1985 to May 1986. The mean (SD) age was 62 (10) years (range 29–76 years); only eight patients were less than 50 years old. Fifteen patients also had aortic regurgitation (grades

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3+ or more) and two of these had mitral regurgitation (grades 3+ or more).[9] In addition, one patient had combined mitral stenosis and regurgitation, one had mitral regurgitation, and one had a prosthetic mitral valve.

Coronary artery stenoses (>50% luminal reduction) were found in 29 (42%) patients; two of these were less than 60. The angiographic ejection fraction ranged from 23 to 90% (mean (SD) 69 (13) %) and the stroke volume from 30 to 179 (mean 75 (27)) ml. The patients were in sinus rhythm, except for three with atrial fibrillation. To analyse the Doppler and catheterisation data we used an average of at least three heart cycles (10 cycles for the patients with atrial fibrillation). The Doppler examination was performed in all patients <48 hours before catheterisation (usually the day before). All patients were clinically stable in the time between the two examinations. The mean (SD) heart rates during the Doppler and catheterisation examinations were 73 (16) (range 49–112) and 73 (15) (range 45–112) beats/min. No patient was excluded from the study because of unsatisfactory Doppler data.

DOPPLER ECHOCARDIOGRAPHY

The continuous wave Doppler examination was performed with an IREX Meridian TM system with a 2 MHz independent transducer and a combined 2–3/3·5 MHz Doppler and cross sectional echo transducer. Measurements of the ascending aortic jet were routinely done from the suprasternal or right parasternal windows with the independent transducer and from the apical window with the combined and/or independent transducer. Optimum Doppler recordings were obtained by locating the signal of highest audible frequency that gave the most clearly defined spectral velocity envelope and maximal velocity. Estimator functions were not used. We did not correct for a presumed angle between the Doppler beam and the maximum aortic jet.

The maximum velocity was assessed manually and converted to the instantaneous maximum pressure gradient by the modified Bernoulli equation[10]: $\Delta P = 4V^2$, where ΔP = pressure gradient (mm Hg) and V = velocity of the blood (m/s). The mean gradient was derived from the IREX Meridian measurement and an analysis software package that integrates the spectral velocity envelope at every 10 ms and calculates the mean of the instantaneous gradients derived from the above equation.

CARDIAC CATHETERISATION

The procedures were done from the percutaneous femoral approach. The left ventricle was catheterised by the retrograde or transseptal technique. Cardiac output was measured by the thermodilution method, left ventricular angiography was performed in the 30° right oblique projection, and aortography in the 45° left oblique position. Selective coronary angiography (Judkins technique) was done in all patients aged over 30.

Intravascular pressure was recorded through fluid filled catheters with the transducer at the midaxillary level. In 55 patients the aortic valve gradient was measured from the immediate pullback pressure in the ascending aorta superimposed on the ventricular recording. Simultaneous pressure tracings obtained by the transseptal technique were used in 14 patients. We measured the instantaneous maximum, the traditional peak to peak, and the mean systolic pressure gradients. The aortic valve area was calculated from the Gorlin equation.[8] In patients with clinically significant valve regurgitation we used single plane angiographic assessments of stroke volume[11] instead of the thermodilution data to calculate the area.

STATISTICAL ANALYSIS

Data are expressed as mean (1 SD). All tests were two tailed and the level of significance was set at $p < 0·05$. Student's *t* test was used to compare mean differences between groups. The agreement between Doppler and catheterisation gradients was evaluated according to the method of Altman and Bland.[12] We used stepwise regression analysis, forwards and backwards[13] (MINITAB statistical software[14]), to assess the possible influence of independent variables on the differences between Doppler and catheterisation gradients. A non-linear relation was derived for the association between pressure gradients and the aortic valve areas after logarithmic transformation to fit linear regression.[14]

Results

AGREEMENT BETWEEN PRESSURE GRADIENTS

There was good agreement between the maximum Doppler gradients and those measured by catheterisation (fig 1a). The maximum Doppler gradients ranged from 16 to 144 mm Hg (mean 80 (33) mmHg) and those at catheterisation from 19 to 182 mm Hg (mean 85 (37) mm Hg). The mean Doppler gradients ranged from 10 to 102 mm Hg (mean 51 (23) mm Hg) and the mean catheterisation gradients from 11 to 141 mm Hg (mean 58 (28) mm Hg). Again these were in close agreement (fig 1b). For one obvious outlier, however, a mean catheterisation gradient of 141 mm Hg was estimated by Doppler to be 85 mm Hg. The corresponding maximum gradients were 182 and 148 mm Hg. The generally good agreement between the maximum and mean gradients obtained by the two methods also applied to the 15 patients with aortic stenosis and regurgitation (fig 1a and b).

DIFFERENCE BETWEEN PRESSURE GRADIENTS

The maximal Doppler ($p < 0.001$) and catheterisation gradients ($p < 0.001$) were significantly higher and different from the peak to peak gradients at catheterisation, which ranged from 4 to 153 mm Hg (mean 66 (35) mm Hg). Compared with the catheterisation gradients, the Doppler technique systematically underestimated both the maximum and the mean gradients, particularly in the high range. This caused on average a small but significant pressure difference between the two methods for

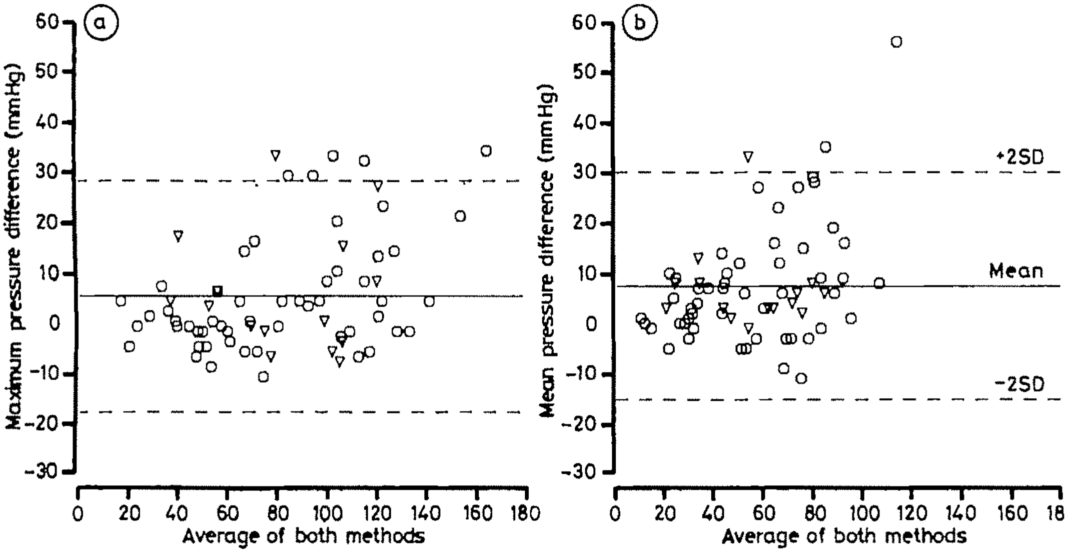

Fig 1 *The difference between (a) maximum and (b) mean catheterisation and Doppler systolic pressure gradients in relation to the average pressure measured by both methods.* ○ *pure aortic stenosis (n = 54);* △ *aortic stenosis and regurgitation (n = 15).*

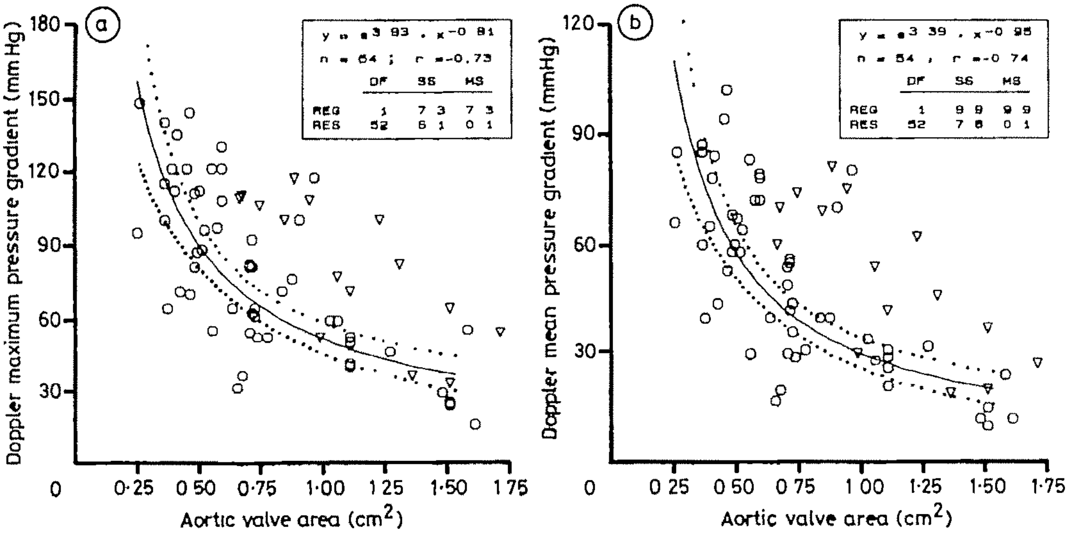

Fig 2 *The relation of systolic pressure gradients to the aortic valve area (a) Maximal Doppler gradients versus aortic valve areas. (b) Mean Doppler gradients versus aortic valve areas. The non-linear correlation with 95% confidence interval was calculated for patients with pure aortic stenosis only (n = 54). DF, degrees of freedom; MS, mean square; SS, sum of squares; REG, regression; RES, residual See fig 1 for symbols.*

both the maximum ($p < 0.001$) and mean gradients ($p < 0.001$). In stepwise regression analysis this difference could not be explained by age, sex, stroke volume, ejection fraction, the presence of coronary artery disease, severity of aortic regurgitation, or differences in heart rate between the two examinations. There were too few (three) patients with atrial fibrillation for this feature to be included as an independent variable in the stepwise regression analysis.

RELATION OF PRESSURE GRADIENTS TO AORTIC VALVE AREAS

As predicted by the Gorlin equation,[8] a negative curvilinear function described the relation between the maximum ($r = -0.73$) and the mean ($r = -0.74$) Doppler gradients and the aortic valve areas at catheterisation in the patients with pure aortic stenosis ($n = 54$) (fig 2a and b). This correlation decreased when the patients who also had aortic regurgitation ($n = 15$) were included ($r = -0.65$ and -0.66 respectively). There was a large scatter of pressure gradients above and below the correlation lines. For critical areas $\leqslant 0.75$ cm^2 the range of maximum and mean Doppler gradients was 31 to 144 and 17 to 102 mm Hg respectively. The scatter of the maximal and peak to peak catheterisation gradients in relation to the areas was similar (detailed data not shown).

Discussion

The area of the aortic valve is usually considered to be more reliable than the systolic pressure gradient in predicting the need for valve replacement in patients with aortic stenosis.[7] Although Doppler echocardiography accurately detected the transvalvar gradients, the curvilinear relation between the pressure gradients and the aortic valve areas was less exact. In fact, the range of Doppler gradients for a given area was wide. According to the Gorlin formula,[8] this scatter of gradients is the result of variations in transvalvar flow. It could not be explained by the small differences between the Doppler and catheterisation gradients. When transvalvar flow is low small valve areas can be seen with low gradients, especially in patients with poorly contracting or small hypertrophied left ventricles. Valve areas that are larger than predicted from pressure gradients are seen when the transvalvar flow is increased, as in patients with aortic regurgitation and other high output cardiac states.[7 10]

Although the presence of aortic regurgitation, or other causes of a high stroke volume, did not significantly influence the measurement of Doppler pressure gradients in this study, the aortic valve areas could not be predicted from the pressure gradients alone in such patients. Thus high or low transvalvar flow severely limits the accuracy of the Doppler method in assessing the aortic stenosis. Furthermore, during follow up an unchanged gradient does not exclude the possibility of a significant decrease of the aortic valve area. However, the development of Doppler techniques that non-invasively assess the cardiac output[15 16] or the actual aortic valve area[17–19] largely overcomes these limitations of the Doppler method.

Despite the close agreement between the transvalvar pressure gradients obtained by Doppler and catheterisation the Doppler technique systematically underestimated the results of catheterisation data, particularly gradients in the high range. This caused the Doppler gradients to be on the average slightly, but significantly, lower than those at catheterisation. In stepwise regression analysis the small pressure difference between the two methods was unrelated to age, sex, stroke volume, ejection fraction, the presence of aortic regurgitation, coronary artery disease, or differences in heart rate between the two examinations.

Previous studies that assessed various subgroups alone,[2] or combined with linear regression analysis[4 5] did not find that the correlation coefficients were influenced by low cardiac output, left ventricular function, or associated coronary artery disease. A recent study, however, that used the same statistical method, found that experience with the Doppler technique, the presence of aortic regurgitation, and atrial fibrillation did.[6] Stepwise regression analysis avoids splitting the study population into small subgroups and thus may partly explain why our results were different. The good agreement between the Doppler and catheterisation gradients in this study might, however, be partly the result of having few patients in the study group with atrial fibrillation. On the other hand, we did include consecutive patients and did not exclude any Doppler data from the analysis. Thus we found that experience with the technique and the use of several transducer positions seem to be more important than other physiological factors for obtaining a reliable Doppler gradient.

Technical errors may contribute to differences in measuring gradients. These include the fidelity of the fluid filled catheter system, catheter induced artefacts, and phase shifts between non-simultaneous measurements of left ventricular and aortic pressure.[4] On the other hand, the Doppler results are influenced by angle errors, experience, the use of multiple transducer positions, and assumptions in the modified Bernoulli equation.[2 10] Although the Doppler and catheterisation measurements were not simultaneous in our study, this seems to have had little effect on their compatibility.

We conclude that Doppler echocardiography is accurate in assessing the systolic transvalvar pressure gradients in patients with aortic stenosis and is less influenced by physiological factors than previously reported. Although there is a significant negative curvilinear relation between Doppler gradients and aortic valve area, we found that, in contrast with earlier reports,[3 5] this association is not accurate enough to be the basis for a decision about valve replacment if the transvalvar flow is not also assessed.

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Cardioangiographic findings in patients with arrhythmogenic right ventricular dysplasia

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SUMMARY The dimension, contractility, and regional wall motion of the right and left ventricles were scored on the angiograms of 13 patients with arrhythmogenic right ventricular dysplasia. In 10 patients the right ventricle was enlarged, in eight the contractility of the right ventricle was reduced, and in all but one patient there were regional wall motion abnormalities of the right ventricle. The most common abnormality of regional wall motion was mild hypokinesia. There were bulging or dyskinetic areas in seven patients. Regional wall motion abnormalities of the left ventricle were found in five patients, two of whom also had bulging or dyskinetic areas. The reproducibility of right ventricular dimension, contractility, and regional wall motion scores was generally fair but varied unexpectedly both within and between two observers (Kendall's Tau 0·38–0·92). The score values of regional wall motion for some of the segments differed considerably within and between observers. One of the observers consistently gave higher scores than the other.

These data suggest that a more objective approach is needed for evaluating angiographic changes in arrhythmogenic right ventricular dysplasia.

Patients with arrhythmogenic right ventricular dysplasia usually have recurrent right ventricular tachycardia[1-3] and variable replacement of right ventricular myocardial tissue by adipose and fibrous tissue.[4-6] The clinical diagnosis is based on demonstration of morphological changes in the right ventricular wall in the absence of any other identifiable structural heart or pulmonary disease.[1 2] Although right ventricular wall motion abnormalities can also be detected by echocardiography,[7-9] radionuclide angiography,[7 10 11] and cine-computed tomography,[12] right ventricular angiography is generally regarded as the standard in the diagnosis of arrhythmogenic right ventricular dysplasia.[2 3 8] Recently, certain regional right ventricular angiographic characteristics were suggested as diagnostic criteria for this disorder.[13] It is not known how reproducible these measurements are, however.

The objective of our study was to describe and evaluate the angiographic findings in a group of patients with arrhythmogenic right ventricular dysplasia, and to try to assess the reproducibility of global and regional right ventricular findings within and between observers.

Patients and methods

We studied 13 patients (nine men and four women, mean age 34) referred with ventricular tachycardia and with a history and clinical findings consistent with arrhythmogenic right ventricular dysplasia (table 1). All patients had ventricular tachycardia with a left bundle branch block configuration. Electrophysiological testing in 10 confirmed the right ventricular origin of the ventricular tachycardia. No patient was in cardiac failure at the time of the study. Arrhythmogenic right ventricular dysplasia was diagnosed on the basis of the characteristics of ventricular tachycardia, the results of signal-averaged surface electrocardiogram and electrophysiological studies, echocardiographic findings, and radionuclide angiography or cinecardioangiography or both. No patient had clinical or angiographic evidence of coronary artery disease or

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Table 1 *Clinical details and a summary of right ventricular wall motion abnormalities in 13 patients with arrhythmogenic right ventricular dysplasia*

Case No	*Age (yr) and sex*	*Symptom duration (months)*	*ECG T inv*	*Q waves*	*X ray heart size*	*AA treatment during study*	*Total RW-MS*
2	25 M	144	V1–V4	0	↗ (RV+)	0	25
3	31 M	288	V1–V4	V6	↗ (RV+)	Quinidine, digitalis	23
7	41 M	3	V1, III	0	N	Sotalol	13
8	15 M	5	V1–V4, aVF–III	0	N	0	9
9	41 F	31	0	0	N	Mexiletine, disopyramide	10
10	35 M	84	V1–V4, III	aVF–III	↗	Flecainide	9
11	25 M	7	V1–V3	V1–V3	N	Metoprolol, tocainide	30
13	49 F	300	V1	0	N	Flecainide	11
14	49 F	48	V1–V2	0	N (RV+)	0	12
15	40 M	4	V1	0	N	Metoprolol	8
16	25 M	48	V1–V2, aVF–III	0	↗ (RV+)	0	24
17	36 M	12	V1	0	↗ (RV+)	0	13
19	31 F	12	V1	0	N	Sotalol	16

Heart size was measured by calculating the relative cardiac volume. AA, antiarrhythmic; N, normal; RV+, prominent right ventricle; RWMS, right ventricular regional wall motion score; T inv, T wave inversion; ↗, increased heart size.

other organic heart disease. The long term follow up of ten patients in this series has been reported earlier, and the case numbers assigned to them have been retained.[14]

CARDIOANGIOGRAPHY

Right ventricular cineangiography was performed from the femoral approach with an 8 F Grollman catheter. Contrast was injected into the right atrium in three patients, into the right ventricle in seven, and into both cavities in three patients. The left ventricle was visualised in the levophase after injection of radio-opaque dye into the right ventricle in five patients and by selective left ventricular angiography in eight patients. Approximately 50 ml of Isopaque Coronar (metrizoate), 370 mg I/mol, was injected at a rate of 13 ml/s. Angiograms were acquired at 75 frames per second and presented in both right anterior oblique and left anterior oblique projections. The ventriculograms were reviewed independently by experienced observers who did not known the patient's identity and clinical status. The evaluations were performed according to a standardised protocol, but the observers were also instructed to comment on abnormal findings not included in the protocol. Right and left ventricular dimensions were visually assessed as normal, mildly, moderately, or considerably enlarged (scored 1, 2, 3, and 4 respectively). The overall contractility was classified as normal, fair, poor, or as severely hypokinetic (scored 1, 2, 3, and 4 respectively).

To evaluate regional wall motion, the right and left ventricles were divided into segments (fig 1). Each segment was classified as normal, mildly, or severely hypokinetic, akinetic or dyskinetic (scored as 1, 2, 3, 4, and 5 respectively). The right ventricular outflow tract was classified as normal or wide (scored as 1 and 5 respectively). Segment scores were added, and the wall motion score of the right ventricle was expressed numerically. The minimum/maximum wall motion score for the right ventricle was 8/40. The left ventricular ejection fraction, measured in 11 patients, was calculated by the single plane area length technique.[15] Each patient had coronary arteriography. In some patients medication could not

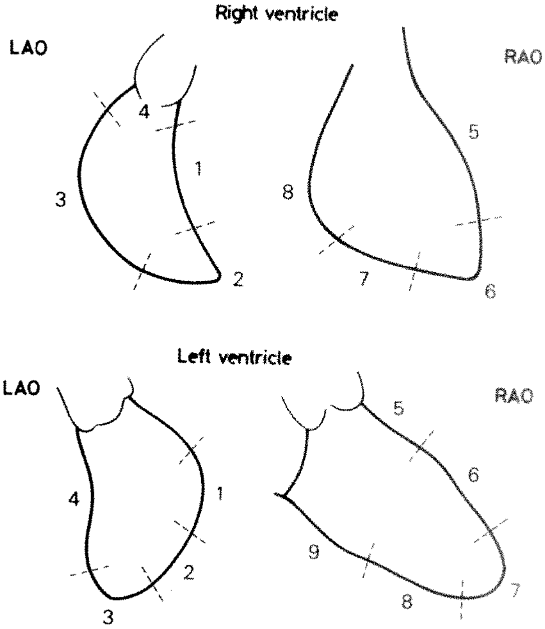

Fig 1 *In the left anterior oblique (LAO) view each ventricle was divided into four segments. In the right anterior oblique (RAO) view the right ventricle was divided into four and the left ventricle into five segments.*

Table 2 *Right ventricular regional wall motion scoring in 13 patients with arrhythmogenic right ventricular dysplasia*

Region	*Normal*	*Mild hypokinesia*	*Severe hypokinesia*	*Akinesia*	*Dyskinesia (wide)*	*Total abnormalities (cases)*
LAO:						
R1	9	2	1	0	1	4
R2	7	4	1	0	1	6
R3	9	0	2	1	1	4
R4	7	—	—	—	(6)	6
RAO:						
R5	9	4	0	0	0	4
R6	8	4	0	0	1	5
R7	6	4	1	1	1	7
R8	5	3	1	0	4	8
Total (regions)	60	21	6	2	9 (6)	

The numbers of patients are shown unless stated otherwise. Mild hypokinesia was the most frequent regional wall motion abnormality (21 regions); this was evenly distributed among the segments in the right ventricle. Dyskinesia was most often seen in the inferobasal region (R8), which was also the most commonly involved region in arrhythmogenic right ventricular dysplasia. LAO, left anterior oblique view; R, right ventricular segment; RAO, right anterior oblique view.

be safely discontinued at the time of the study (table 1).

STATISTICAL METHODS

To assess the reproducibility of right ventricular findings, between and within observers, each angiogram was interpreted both by a pair of observers on one occasion (observers 1) and also by one observer (observer 2) on two occasions separated by an interval of several weeks. We assessed the reproducibility by calculating Kendall's Tau$_b$, which is a measure of rank correlation.[16] Kendall's Tau was also used to test the null hypothesis of zero correlation in the underlying population.

To assess whether there was any bias in awarding high or low scores we compared the proportions of high scores for each of the ten variables (dimension, contractility, and regional wall motion in segment R1 to R8) awarded by observers 1 and 2 and between the first and second interpretation of observer 2. Scores of 3 and 4 or 4 and 5 were defined as high for global and regional changes respectively. The two sided exact binomial test (sign-test) was used to compare the proportions.

Results

MORPHOLOGICAL FINDINGS

The following angiographic findings were reported by the two observers. The right ventricle was enlarged in ten patients, eight of whom also had a reduced overall contractility. All but one patient (case 15) had abnormal regional wall motion of the right ventricle. This patient, however, was twice judged by observer 2 to have abnormal wall motion on angiography. The most frequent local wall motion abnormality was a

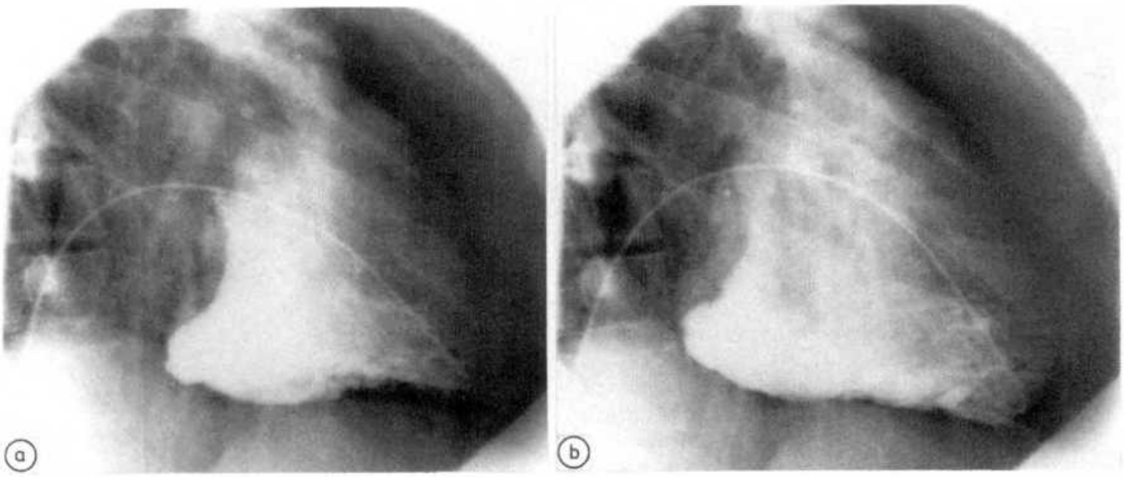

Fig 2 *Right ventriculogram of patient 16 from the right anterior oblique view. There are dyskinetic outpouchings in the inferior segments of the right ventricle where stagnation of contrast is evident. (a) End systole and (b) end diastole.*

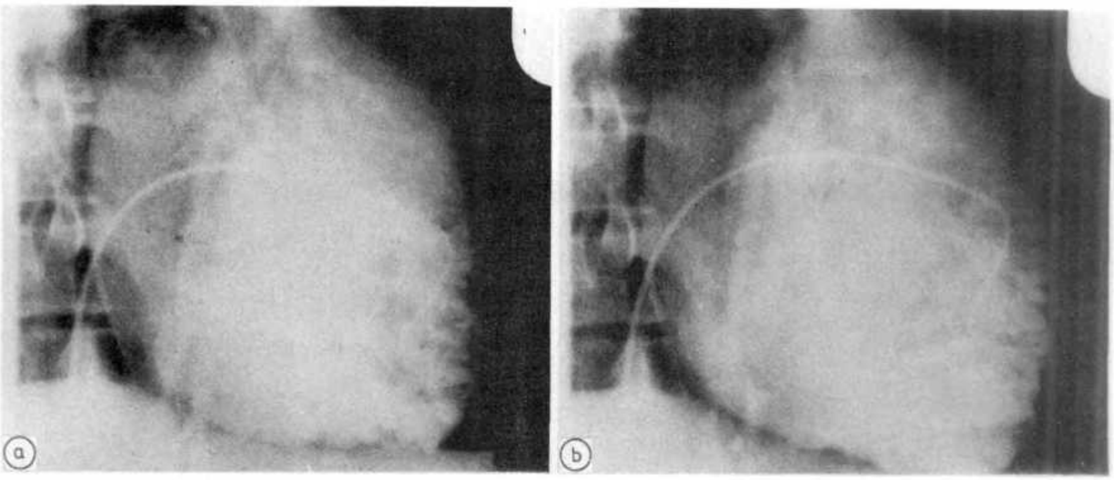

Fig 3 *Right ventriculogram of patient 3 from the right anterior oblique view. Note the fissuring of the anterior wall. (a) End systole and (b) end diastole.*

mild hypokinesia (table 2). Most changes in regional wall motion were found in the inferior portion of the right ventricle (segments R7 and R8). Pronounced bulging, outpouchings, or dyskinetic areas were found in seven patients. These changes were most common in the inferior segments (fig 2), but were also seen in the anterolateral, septal, and apical regions (table 2). Elimination of dye in the dyskinetic regions was always slow. Deep fissuring of the anterior right ventricular wall was evident in one patient (case 3) (fig 3). A wide right ventricular outflow tract was found in six patients. The right ventricle was considerably trabeculated in two patients (cases 2 and 3) (fig 4). In two patients (cases 8 and 13) abnormal regional wall motion was recognised only in one projection; this was the left anterior oblique and right anterior oblique respectively.

The left ventricle was slightly or moderately enlarged in three patients (cases 3, 11, and 16), all of whom had a considerably enlarged right ventricle. The overall contractility was classified as fair in two patients (cases 16 and 19) and poor in one (case 3), but it was normal in all other patients. Abnormal regional wall motion of the left ventricle was found in four patients, all of whom had evidence of functional impairment and three of whom had only mild hypokinesia. Outpouchings or dyskinetic regions were found in only one patient (case 3). This patient

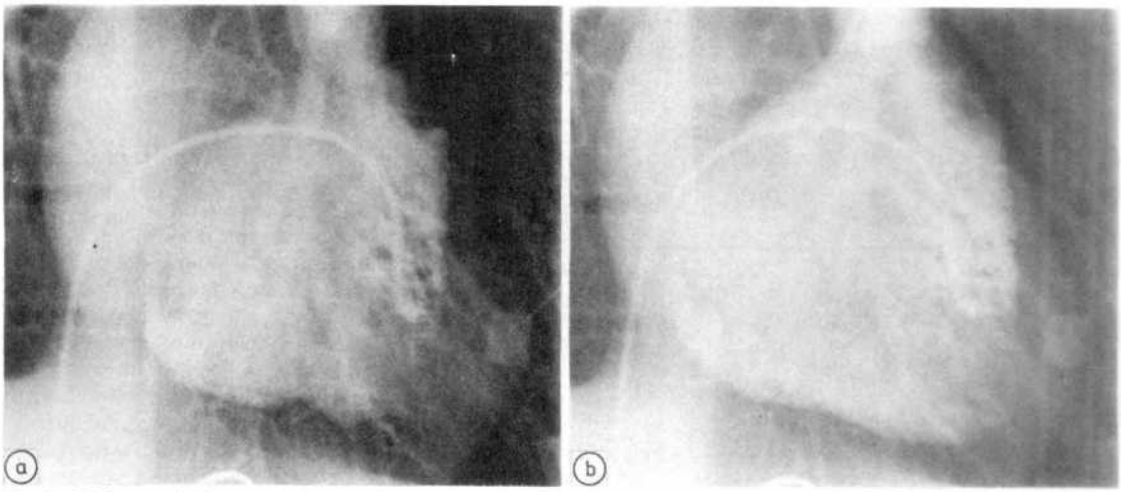

Fig 4 *Right ventriculogram of patient 2 from the right anterior oblique view. The right ventricle is enlarged, hypokinetic, and considerably trabeculated. There is dyskinesia in the inferobasal segments. (a) End systole and (b) end diastole.*

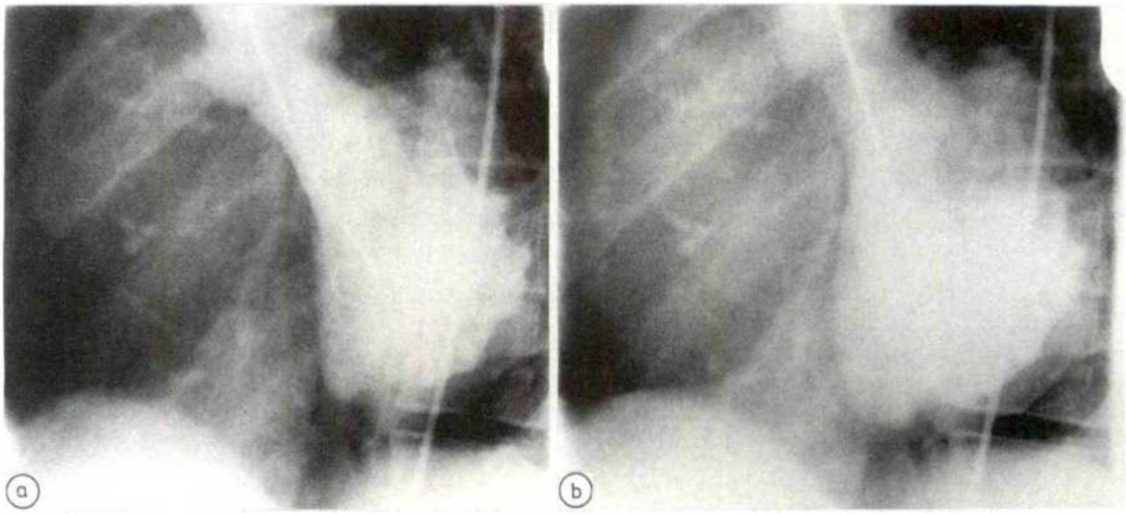

Fig 5 *Left ventriculogram of patient 3 from the left anterior oblique view. There is dyskinesia in the posterior segments. (a) End systole and (b) end diastole.*

also had pronounced abnormalities of right ventricular wall motion (fig 5), and the posterior region of the left ventricle was as trabeculated as the right. The left ventricular ejection fraction was normal (> 60%) in all but one patient (43% in case 3). There was no important tricuspid or mitral valve regurgitation or other valve abnormality. The coronary arteriograms showed no significant stenosis.

REPRODUCIBILITY OF RIGHT VENTRICULAR FINDINGS

Table 3 shows the reproducibility of right ventricular findings within and between observers. Although there was a statistically significant positive correlation between dimension scores, contractility scores, and, in most segments, between regional wall motion scores within and between observers, reproducibility as measured by Kendall's Tau was generally only fair. The reproducibility of regional wall motion scores within and between observers varied widely among the different segments (fig 6). It was poor for segments R2, R3, and R6 between observers 1 and 2, and also for segment R6 between the first and second interpretations of observer 2 (table 3).

Table 3 *Values of Kendall's Tau*$_b$

	Interobserver correlation	*p value*	*Intraobserver correlation*	*p value*
Dimension	0·92	0·0002	0·62	0·0123
Contractility	0·65	0·0131	0·70	0·0089
R1	0·55	0·0403	0·82	0·0036
R2	0·38	NS	0·76	0·0050
R3	0·48	NS	0·63	0·0160
R4	0·85	0·0031	0·63	0·0304
R5	0·94	0·0007	0·54	0·0433
R6	0·43	NS	0·47	NS
R7	0·73	0·0044	0·71	0·0061
R8	0·59	0·0213	0·68	0·0095

R, right ventricular segment; NS, not significant.

The differences in score values within and between observers were considerable for some segments. For example segments R7 and R8 were both scored as 5 by observer 1 while observer 2 scored them as 2 and 1 respectively. The proportion of high and low scores differed significantly between observers 1 and 2, the former consistently gave higher scores ($p < 0{\cdot}05$). This pattern of preference towards high or low scores was not seen between the interpretations from observer 2 (NS).

Discussion

Most cardiologists use selective right ventriculography to diagnose arrhythmogenic right ventricular dysplasia, especially in patients with atypical clinical signs or electrocardiographic findings.[1,2] The right ventricular angiographic abnormalities in this disorder have been described as localised bulges or diverticular outpouchings, a feathery appearance of or non-opacified areas in the outflow tract, deep fissuring or cauliflower-like appearances of the anterior wall, and slow clearance of dye adjacent to poorly contracting areas.[2,17,18] The segmental impairment of the right ventricle has also been described in terms of regional hypokinesia, akinesia, or dyskinesia.[3,19,20] In a recent review of angiograms in eight patients with arrhythmogenic right ventricular dys-

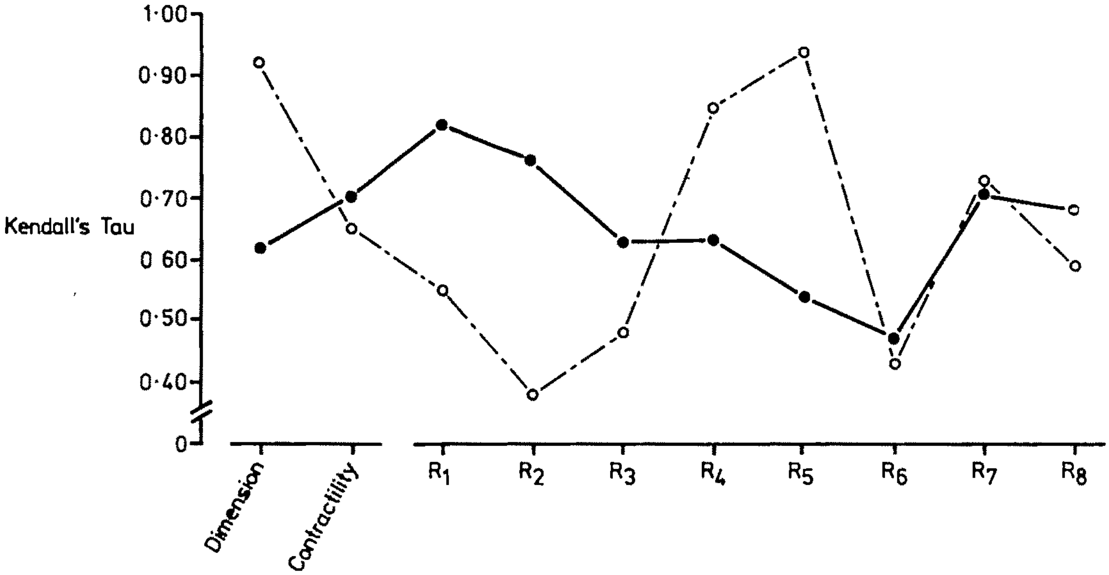

Fig 6 *Degree of correlation, as measured by Kendall's Tau, for right ventricular dimension, contractility, and regional wall motion in eight segments (R1–R8), within (dotted lines) and between (continuous lines) observers.*

plasia, the presence of four predetermined regional changes was assessed and diagnostic criteria were established.[13] Fissuring distal to the moderator band, stagnation of contrast in the inferior regions, and irregular opacification of the infundibulum were found in most patients. None of these lesions was found in a comparable group of cases with dilated cardiomyopathy, and this emphasises the segmental nature of the morphological changes in arrhythmogenic right ventricular dysplasia.

The right ventricular findings in the present group of patients accorded with earlier descriptions of angiographic changes in arrhythmogenic right ventricular dysplasia. The effect of antiarrhythmic drugs on cardiac contractility is unpredictable in an individual patient and such agents may have accounted for the reduced global contractility in some of our patients. The functional impairment of the left ventricle was, however, minor and limited to a few patients, which argues against any important effect on the observed regional wall motion abnormalities of the right ventricle.

Unlike previous studies, the angiograms in the present report were systematically examined according to a standardised protocol in order to obtain unbiased interpretations. Moreover, right ventriculography was performed in both the right anterior oblique and left anterior oblique projections—in some studies only the right view was used[13] and in others the views used were not clearly stated.[2 5] If only right anterior oblique projections are used, the geometry of the right ventricle may make it difficult to exclude right ventricular wall motion abnormalities with confidence. This was demonstrated in one of our patients in whom a localised lesion was recognised in the left anterior oblique view only. This shows that it is important to use both the right anterior oblique and left anterior oblique views for radiography of the right ventricle. Previous studies found that the most frequent areas of localised lesions were the infundibulum, the apex, and the inferior wall of the right ventricle.[2] In our study the inferior wall was most commonly affected, whereas there was an even distribution of regional changes among the other segments.

The types of regional wall motion abnormalities in the left ventricle were similar to and contiguous with those on the right side. Although there was a relatively large number of left ventricular abnormalities in the present series, most of them were mild. It is not known how commonly the left ventricle is affected in arrhythmogenic right ventricular dysplasia; however, it may be more than previously recognised.[10 21] In the largest series published to date only one out of 22 patients showed angiographic evidence of left ventricular abnormalities.[2] Radionuclide angiography during exercise showed that in patients with arrhythmogenic right ventricular dysplasia the left ventricle was affected more often than previously recognised.[10] The frequency with which left ventricular abnormalities are detected may thus be a reflection of the method used. None the less, since there is evidence of a close interrelation between the functions of the right and left ventricles,[22] it is conceivable that the left ventricular involvement seen in our patients was secondary to a compromised right ventricular function, particularly as the segments affected adjoined the right ventricle.

The sensitivity and the specificity of angiographic changes in identifying patients with arrhythmogenic right ventricular dysplasia are not known, and will presumably be difficult to assess. There are no published reports of evaluations of regional wall motion by right ventricular angiography in normal subjects. Owing to the high radiographic exposure, we did not consider it ethical to perform angiography in healthy individuals. The assessment of the reproducibility of right ventricular angiographic estimations within and between observers was thus all the more important, particularly because as far as we know this aspect has not been studied before. Since our data consisted of non-numerical observations (ranked classes, scores) any statistical computation based on numerical operations of the data beyond ranking was not possible.

The correlation between right ventricular scores was positive and statistically significant both within and between observers for most variables, but it varied considerably among segments. The right ventricular apical segment (R6) gave poor reproducibility both within and between observers for scores of regional wall motion. This segment was also regarded as the most difficult one to image and to evaluate. The larger proportion of high scores reported by observer 1 compared with observer 2 was discouraging but may be related to their different experiences. The most important finding, however, was that there were large differences in the scores for some of the variables, both within and between observers. There is thus a considerable subjective element in the visual assessment of right ventricular changes by angiography. This has important clinical implications for the diagnostic accuracy of qualitatively evaluated angiograms in arrhythmogenic right ventricular dysplasia, especially since right ventricular angiography is the standard method for assessing the diagnostic value of echocardiography and radionuclide angiography in this group of patients.[7,8] The specificity of the angiographic features in arrhythmogenic right ventricular dysplasia is unknown. In addition, right ventricular angiographic abnormalities are not invariably present in these patients[2,23,24] and the diagnosis may not be evident until a histological examination of myocardial tissue is obtained.[2,25] The precise relation between the angiographic features and pathological features remains to be defined. These circumstances may have led some to reject the diagnosis of arrhythmogenic right ventricular dysplasia in patients with right ventricular tachycardia and angiographically proven right ventricular regional wall motion abnormalities unless confirmed by histological data.[26,27]

To sum up, the poor concordance and large differences within and between observers for some of the variables indicate the need for a more objective approach to the evaluation of angiographic changes in arrhythmogenic right ventricular dysplasia. Further work must be done to achieve quantitative standards for angiography. The irregular shape of the right ventricular chamber, however, makes calculations of volumes difficult and relies on geometric assumptions,[28] particularly in patients with arrhythmogenic right ventricular dysplasia, who have regional wall motion abnormalities.

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Accelerated idioventricular rhythm of infundibular origin in patients with a concealed form of arrhythmogenic right ventricular dysplasia

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SUMMARY Five apparently healthy people (aged 16–47) presented with recurrent episodes of accelerated idioventricular rhythm characterised by left bundle branch block and right axis deviation. Clinical history, physical findings, basic electrocardiogram, chest *x* ray, and blood tests were within normal limits in all. Holter monitoring, exercise stress test, and electrophysiological study (in three patients) showed that accelerated idioventricular rhythm was mainly bradycardia dependent, easily suppressed by effort and overdrive pacing, and originated from the outflow tract of the right ventricle. The mechanism could be enhanced automaticity. Data from cross sectional echocardiography (in all patients) and from haemodynamic evaluation (in three) identified structural or wall motion abnormalities of the right ventricle or both without appreciable dilatation of the ventricle. Biopsy specimens of the right ventricular endomyocardium showed fibrosis in one patient, fibrosis and fatty infiltration in the second, and pronounced fatty infiltration in the third.

These results show that some patients with accelerated idioventricular rhythm have right ventricular abnormalities that are typical of the localised and concealed forms of arrhythmogenic right ventricular dysplasia.

Intermittent ectopic idioventricular rhythms at rates of between 40 and 120 beats per minute have been described as accelerated idioventricular rhythms.[1 2]

Accelerated idioventricular rhythm is common in patients with acute myocardial infarction.[1-5] Other conditions causing this arrhythmia include myocarditis, digitalis intoxication, and congenital atrioventricular block.[1 3 6 7] The configuration of the QRS complex during accelerated idioventricular rhythm may be that of either a right bundle branch block or (more often) a left bundle branch block.[1-9] Enhanced automaticity[1] or parasystole[8] have been suggested as possible mechanisms for the arrhythmia. In young people accelerated idioventricular rhythm is rare, and to date there is no correlation established with any well known cardiac pathology.[1 2 8 9]

We report five apparently healthy people presenting with accelerated idioventricular rhythm characterised by left bundle branch block and right axis deviation in whom we found right ventricular abnormalities.

Patients and methods

Five patients (four men and one woman; mean age 26 (range 16–47)), were examined because they had accelerated idioventricular rhythm characterised by left bundle branch block and right axis deviation. None was taking any drug. All were assessed by clinical history, chest *x* ray, blood tests, 24 hour continuous electrocardiographic (Holter) monitoring, and symptom limited exercise stress testing (on a bicycle ergometer with standard protocols). We performed vectorcardiography on all five patients during the arrhythmia (in the supine position), with a Fukuda VA-3G instrument, using the Frank Lead system and dash time interval of 2 ms. Three patients were examined in an electrophysiological and haemodynamic- angiographic study and by right ventricular endomyocardial biopsy.

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Cross sectional echocardiographic images were recorded in all patients on a Hewlett-Packard system and with a 2·5 or 3·5 MHz transducer. Images were obtained in multiple standard views: parasternal, long and short axis; apical, four and two chamber (left and right); and subcostal, four chamber and short axis. Subjects were imaged in either the supine or left lateral recumbent position. The images were examined by two observers for regional wall motion or structural abnormalities of the right and left ventricles or both.[10–13] The right ventricular volume (corrected by the regression equation, according to age and body surface area) was calculated by an area-length method derived from orthogonal planes (apical four chamber and long axis views). A modified Simpson's rule was used to calculate left ventricular volumes from the parasternal short axis and apical two chamber views. The ejection fraction of both ventricles was derived as: $EF = EDV - ESV/EDV$, where EF is the ejection fraction and EDV and ESV are end diastolic and end systolic volumes respectively. Infundibular diameter was determined from the parasternal short axis view of the aortic root. The right ventricular outflow tract was measured from this view as the maximum dimension between the anterior aortic wall and the endocardium of the free wall of the right ventricle.[12]

A haemodynamic-angiographic examination and right ventricular endomyocardial biopsy were performed in the three patients who agreed to the procedure. Haemodynamic study included left and right ventricular angiography, coronary arteriography, and the recording of pressures in various cavities. Angiocardiograms of the right ventricle were obtained in posteroanterior, lateral, and long axis (oblique right and left anterior) projections, for better definition of the infundibulum and posterobasal wall. The angiocardiograms of the left ventricle were performed in the 30° left anterior oblique and right anterior oblique projections. We calculated right ventricular volumes from biplane angiocardiography, using anteroposterior and lateral views (area-length method).[14–16] and left ventricular volumes from monoplane cineangiography using 30° right anterior oblique view.[15] The measured volumes were corrected with a regression equation according to age and body surface. The motion of the right ventricular wall was analysed on the anterior and posterior silhouettes of the infundibulum and on the posterobasal and apical regions. Finally, the trabecular framework was carefully examined.[16] Biopsy specimens of the right ventricular endomyocardium were obtained via the right femoral vein by a standard technique.[17–19] Six biopsy specimens (1–3 mm each), taken from the interventricular septum in each patient, were fixed in formalin, mounted in paraffin wax, and stained with haematoxylin-eosin and azan-Mallory.

Patients 1, 2, and 3 were also studied electrophysiologically; real time records were obtained with an ink jet recorder (Siemens-Elema, Mingograph) with a filter setting of 50–70 Hz for the intracavitary electrocardiograms, at a paper speed of 100 mm/s. Basic conduction (PA, AH, HV) intervals were measured. The right ventricular endocardium was accurately mapped to localise the origin and the successive spread of the accelerated idioventricular rhythm, and to detect late fractionated potentials of QRS. Stimulation was performed with a custom-designed, multiprogrammable stimulator (PPS 500, Medico Italy) with a constant current source and rectangular impulse of 1 ms duration delivered at twice diastolic threshold.

The following protocol was then used to precipitate ventricular arrhythmias, to evaluate the entire conduction system, and to reproduce the

Table 1 *Clinical data and results of chest x ray, electrocardiogram, and exercise stress test in the five patients*

	Case 1	*Case 2*	*Case 3*	*Case 4*	*Case 5*
Age	47	16	21	35	16
Sex	F	M	M	M	M
Follow up (years)	10	2	5	2	2
Symptoms	P, S	P	P	P	P
CT index	0·45	0·53	0·50	0·48	0·45
Inverted T waves*	V1, V2, V3	—	V1	V1	—
AIR					
RR interval	1040	640	840	1000	1000
aQRS	+110	+110	+110	+110	+110
QRS configuration	LBBB	LBBB	LBBB	LBBB	LBBB
QRS configuration in V1	qrS	rS	rS	rS	rS
Exercise test					
Maximal HR	160	170	190	160	180
Double product (HR × BP)	25600	23800	32800	27200	28700
Suppression of AIR at rate:	75	98	102	90	70

AIR, accelerated idioventricular rhythm, BP, blood pressure; CT, cardiothoracic ratio, HR, heart rate, LBBB, left bundle branch block; P, palpitation, S, syncope.
*On basic electrocardiogram

electrocardiographic configuration of the clinical accelerated idioventricular rhythm.

(*a*) Atrial and ventricular pacing at progressively shorter cycles;

(*b*) premature atrial and ventricular stimulation during sinus rhythm (the entire cycle was scanned to the point of atrial and of ventricular refractoriness);

(*c*) Premature atrial and ventricular pacing (S2) during atrial and ventricular pacing with a drive cycle length (S1–S1) of 500 and 700 ms;

(*d*) Double ventricular stimuli (S2–S3) at progressively shorter coupling intervals, during ventricular pacing. S1–S2 was set 50 ms greater than the ventricular refractory period at a given cycle length.

(*e*) Pacing of different sites of the right ventricle (inflow, apex, septum, outflow) was used in an attempt to reproduce the electrocardiographic configuration of the patient's arrhythmia.

Results

Clinical, haematological, and radiological data. All patients had palpitation and in one there was syncope (of doubtful origin) (case 1). Mean follow up, after the detection of the arrhythmia was 4·2 (range 2–10) years. Only patient 1 was treated (successfully) with antiarrhythmic drugs (disopyramide 800 mg/day). Haematological data were all normal. Chest *x* rays showed a cardiothoracic index < 0·53 in all.

BASIC ELECTROCARDIOGRAM, VECTORCARDIOGRAM, EXERCISE STRESS TEST, AND HOLTER MONITORING DATA (TABLE 1)

All patients had normal atrioventricular and intraventricular conduction. We found inverted T waves in V1–V3 in case 1 and in VI in cases 3 and 4. No late potentials were detectable on the surface electrocardiogram. Accelerated idioventricular rhythm had a left bundle branch block configuration and a QRS axis of approximately + 110° in all patients. In V1 four patients had an rS pattern and one (case 1) a qrS pattern (fig 1). The diagrammatic representation of the vector loops were inscribed in a clockwise direction in the frontal plane; in the horizontal plane the initial forces had a clockwise direction, and were followed by counterclockwise rotation; the spatial loop was directed inferiorly and posteriorly. The initial QRS showed considerable slurring in all, and in four (except case 1) this complex was directed anteriorly (fig 2). The accelerated idioventricular rhythm was iterative in four and almost incessant in one (case 2). The cycle length of the accelerated idioventricular rhythm in the five patients varied from 1040 to 640 ms. In two patients the cycle length varied by 50–200 ms in different episodes. The duration of the coupling interval with the preceding sinus beat ranged from 560 to 1480 ms; there were minor variations in the individual patients (40–80 ms) in successive episodes.

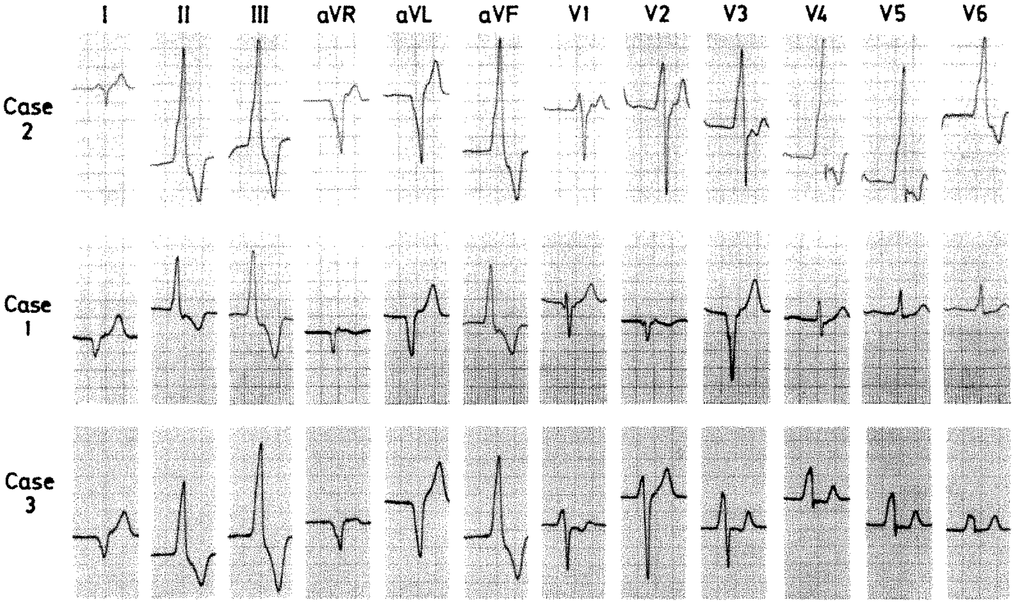

Fig 1 *Twelve lead electrocardiograms from patients 1, 2, and 3 during accelerated idioventricular rhythm. There is left bundle branch block and right axis deviation shown in all. Patients 1 and 3 have an rS pattern in V1 indicating the posterior origin of the arrhythmia.*

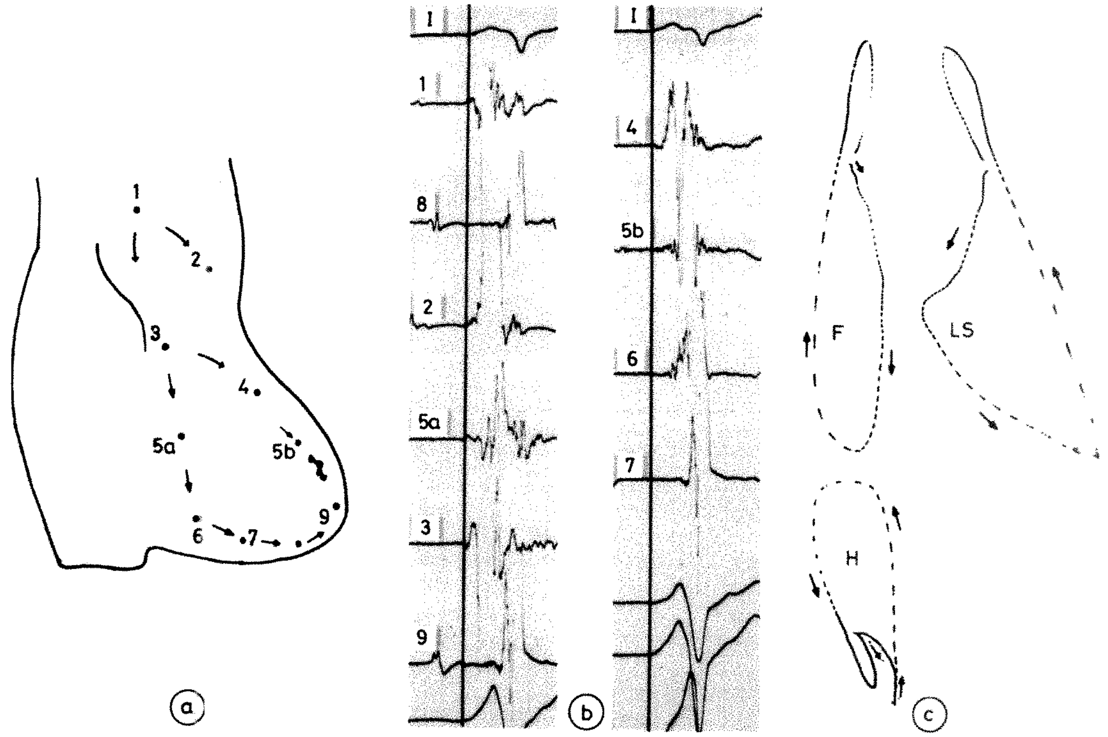

Fig 2 *Right ventricular endocavitary mapping (a, b) and vectorcardiogram (c) of patient 2. (a) Right ventricular activation pattern during accelerated idioventricular rhythm constructed from data are derived from the endocavitary electrocardiographic recordings (b) obtained during the accelerated idioventricular rhythm. Activation began posteriorly in the outflow tract of the right ventricle. The vector loops (c) (F, frontal, H, horizontal, LS, left sagittal) correlated well with the electrophysiological findings.*

In all patients the accelerated idioventricular rhythm was suppressed when the sinus pacemaker accelerated. During the exercise stress test the arrhythmia progressively disappeared in all at a mean sinus frequency of 85 beats per minute. All patients had a normal effort tolerance and none developed major arrhythmias or ST segment alterations.

CROSS SECTIONAL ECHOCARDIOGRAPHY

Cross sectional echocardiography showed right ventricular dilatation in three out of five patients (cases 2, 3, and 4) with a reduced ejection fraction in case 2. The right ventricular outflow tract was dilated in cases 2, 3, and 4. Abnormal regional wall motion or structural alterations or both were detectable in all (see table 2 and fig 3). The left ventricle and the four valves were normal in all.

ELECTROPHYSIOLOGICAL DATA

In three patients (case 1, 2, 3) basic conduction intervals and refractory periods were normal; no late potentials were detectable in the right ventricle. Accelerated idioventricular rhythm was easily suppressed by atrial and ventricular overdrive pacing. Right ventricular mapping and pacing located the origin of accelerated idioventricular rhythm in the outflow tract, posterior ventricle in patients 2 and 3 (fig 2), and anterior ventricle in patient 1. Accelerated idioventricular rhythm or other arrhythmias could not be induced by the above techniques or extrastimuli.

HAEMODYNAMIC DATA

The right ventricle was enlarged in two (cases 2 and 3) of the three patients examined (end diastolic volume = 149 and 122 ml/m^2 respectively) with an ejection fraction of 44 and 52% respectively (fig 4). The right ventricular outflow tract was enlarged and the trabecular framework was abnormal in both; there was bulging of the inferior wall in patient 2 and of the lateral wall in patient 3. Both patients also had abnormal regional wall motion (table 2). The third patient (case 1) had an end diastolic volume and ejection fraction of 70 ml/m^2 and 55% respectively; there was apical hypokinesia, slightly abnormal trabeculae, and bulging of the superoanterior right

Table 2 *Right ventricular angiographic, cross sectional echocardiographic, and histological data*

	Case 1	*Case 2*	*Case 3*	*Case 4*	*Case 5*
Angiography:					
RV EDV (ml/m^2)	70	149	122		
RV EF	55%	44%	52%		
RV structural Abnormalities	e(mild) RVOT = d	e RVIT = d	e LW = d		
RV RWMA	RVIT = a	RVIT = a, b	A:b		
RV biopsy	Fatty infiltration	Mild fibrosis	Fibrosis and fatty infiltration		
Cross sectional echocardiography:					
RV EDV (ml/m^2)	68	135	115	89	66
RV EF	60%	48%	55%	61%	63%
RVOT diameter (normal < 2·5 cm)	2	3·1	2·8	3·6	2·1
RV structural Abnormalities	e(mild) RVOT = d	e RVIT = d	e LW = d	—	f
RV RWMA	RVIT = a	RVIT = a, b	A = a, b	RVIT = d	A = a

RV, right ventricular; RV EDV, right ventricular end diastolic volume (normal value = 81 (12·3) ml/m^2); RV EF, ejection fraction (normal value 51 (8)[14]; RV RWMA, right ventricular regional wall motion abnormalities. Right ventricle was divided into four regions: A, apex; LW, lateral wall; RVOT, right ventricular outflow tract; RVIT, right ventricular inflow tract.
List of RV RWMA and RV structural abnormalities: (a) hypokinesia; (b) akinesia; (c) systolic dyskinesia; (d) diastolic bulging; (e) derangement of the trabecular framework and papillary muscles; (f) altered echogenicity and nodulation of the moderator band.

ventricular wall. The left ventricle and coronary arteries were normal in all.

ENDOMYOCARDIAL BIOPSY OF THE RIGHT VENTRICLE

There was pronounced fatty infiltration with myocardial atrophy in patient 1 (fig 5), mild fibrosis in patient 2, and fibrosis with mild fatty infiltration in patient 3.

Discussion

Accelerated idioventricular rhythm occurs in 12–30% of patients with acute inferior myocardial infarction. It is often seen in the first 12 hours, occurs intermittently for a few hours thereafter, and usually resolves after 24 hours.[1 3-6]

The arrhythmia has also been found in other heart diseases,[1 3 6 7] but has been rare when there is no definite cardiac abnormality. We know of few

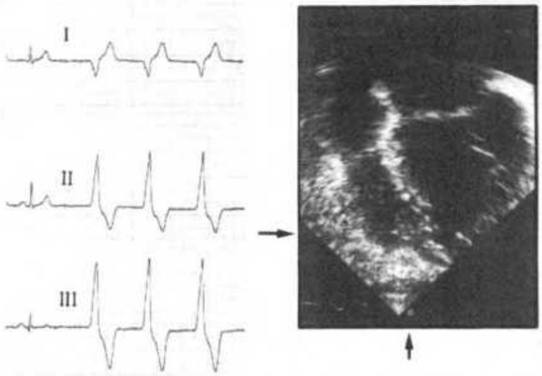

Fig 3 *The electrocardiogram of patient 3 during an initiating episode of accelerated idioventricular rhythm. An apical four chamber cross sectional echocardiographic view of the same patient showing sacculation of the lateral wall of the right ventricle and apical akinesia (see arrows).*

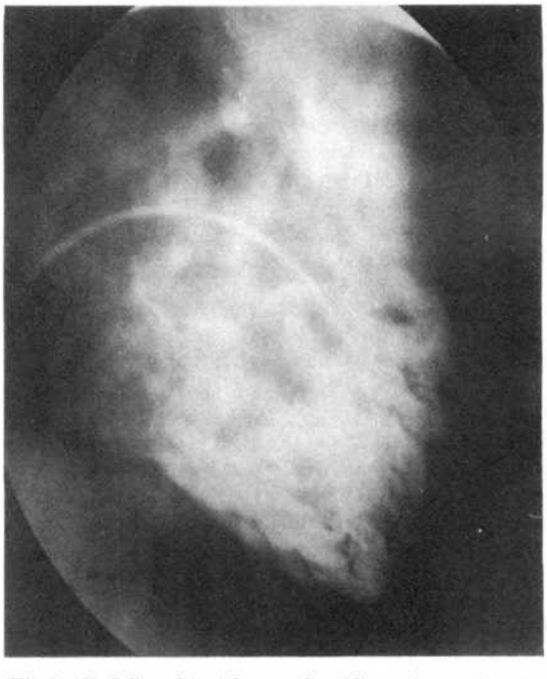

Fig 4 *End diastolic, right anterior oblique (long axis) view of a right ventricular angiogram (patient 2). The right ventricular chamber is slightly dilated (volume 149 ml/m^2, ejection fraction 44%) and there is fissuring of the anterolateral wall.*

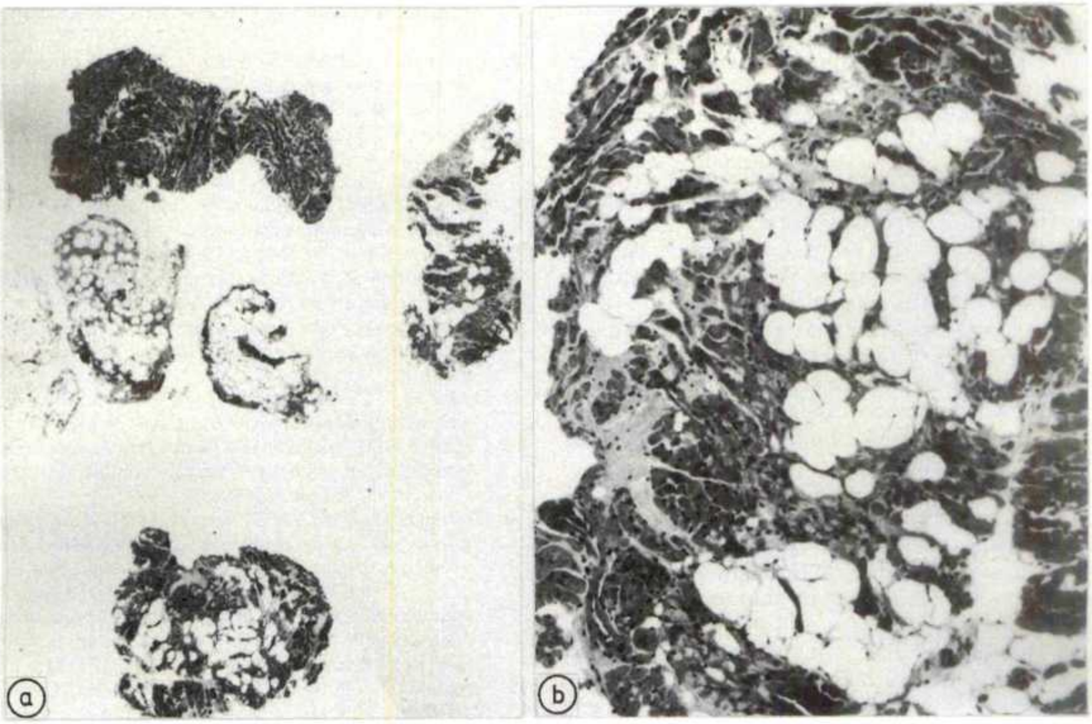

Fig 5 *(a) Endomyocardial biopsy specimens of the right ventricular septum (patient 1). Tissue in three of the six was almost entirely adipose. Haematoxylin-eosin, original magnification × 10. (b) The myocardium was slightly sclerotic and infiltrated by adipocytes. Haematoxylin-eosin, original magnification × 48.*

previously reported idiopathic cases in young healthy people.[1-3,8,9] There is little published information on basic electrocardiography and the QRS configuration in accelerated idioventricular rhythm. Also echocardiographic and angiographic study is limited and the right ventricle, in particular, has not been fully studied in these patients.

All our patients showed a QRS configuration consistent with left bundle branch block and right axis deviation. The accelerated idioventricular rhythm seemed to be bradycardia dependent; it began as an escape rhythm, with different coupling intervals, and it always ended spontaneously after overdrive suppression by sinus rhythm. The RR intervals were uniform during each episode but accelerate or slow in subsequent episodes, suggesting a sympathetic or parasympathetic influence on the ectopic focus. Accelerated idioventricular rhythm always disappeared during effort when a critical rate (usually 75–102/min) was reached. The rhythm was not inducible nor was it accelerated by electrophysiological techniques. All the above patterns were typical of an ectopic automatic rhythm without parasystole and reentry.

Standard electrocardiography, vectorcardiography, and endocardial mapping during the electrophysiological study showed that the accelerated idioventricular rhythm originated in the right ventricular outflow tract (figs 1 and 2). In all our patients data from the cross sectional echocardiography and haemodynamic-angiographic studies excluded valvar, left ventricular, and coronary heart diseases and showed structural or wall motion abnormalities of the right ventricle or both. Endomyocardial biopsy specimens showed fibrosis and/or fatty infiltration, particularly in case 1 (fig 5).

These alterations may be associated with minor concealed forms of arrhythmogenic right ventricular dysplasia.[17-22] This disease has many forms—from a generalised involvement of the entire ventricle[23-25] with global dilatation, altered haemodynamic function, and reduced ejection fraction, to mild focal lesions characterised by an almost normal clinical picture and normal features on invasive and non-invasive investigation.[13,17,20-22,26-31] Only a careful examination of the right ventricle, with endomyocardial biopsy in selected cases, can detect structural and/or regional wall motion abnormalities, which might represent a forme fruste of the condition.

Right ventricular dysplasia should always be suspected in patients with ventricular arrhythmia (sustained and transient ventricular tachycardia, couplets, isolated premature ventricular complexes) when left bundle branch block and right axis deviation suggest an abnormal right ventricular outflow tract.[20–27 29 32–34] We believe that in other reported cases of "idiopathic" ventricular arrhythmias the ventricular outflow tract could have been responsible for the arrhythmia, especially "concealed" forms, but unfortunately the right ventricle was rarely examined in detail,[35–40] because the left ventricle and coronary arteries received the most attention.

Our report suggests that accelerated idioventricular rhythm, in our cases caused by enhanced automaticity, could be an arrhythmia associated with concealed forms of arrhythmogenic right ventricular dysplasia, when the QRS indicates a right ventricular infundibular origin.

Follow up of our patients has confirmed that this type of automatic ventricular arrhythmia is benign and does not usually need to be treated. But because we found an abnormality in the right ventricle such patients should continue to be monitored.

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Delayed improvement in exercise capacity after cardioversion of atrial fibrillation to sinus rhythm

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SUMMARY In some patients symptoms improve after the restoration of sinus rhythm from atrial fibrillation. To assess the size and mechanism of such change, exercise capacity and pulsed Doppler left ventricular inflow velocities were assessed in 20 patients with established atrial fibrillation. Treadmill exercise capacity was assessed by measuring maximal oxygen consumption and anaerobic threshold before and on day 1 and 28 days after elective DC cardioversion. The relative contribution of atrial contraction to left ventricular filling was determined by relating the maximum height of the A wave to the maximum height of the E wave (A/E) of the Doppler velocity time curve. Cardioversion was successful in 14 patients. Maximal oxygen consumption and anaerobic threshold were unchanged on day 1 and increased by day 28 in all 14 patients. The percentage improvement was inversely related to the baseline values; however, the absolute improvement was small in all patients. The mean A/E ratio increased significantly from day 1 to day 28 in all 14 patients.

Thus the restoration of sinus rhythm was associated with a delayed improvement in exercise capacity that may in part be due to a slow improvement in atrial contractility and peak cardiac output after cardioversion.

Direct current cardioversion of atrial fibrillation is often performed to improve cardiac output and exercise capacity by regularising the heart beat and restoring the atrial systolic contribution to ventricular filling. The magnitude and time course of this improvement are controversial and the relative contribution of atrial systole to stroke volume is still uncertain.[1-4] The purpose of the present study was to assess the mechanism and size of the increase in exercise capacity after cardioversion of atrial fibrillation to sinus rhythm.

Patients and methods

We studied 20 patients (18 men and 2 women; mean (SD) age 58(8) years). Atrial fibrillation had been present for 6–14 weeks and was associated with previous aortic or mitral valve surgery in five patients (performed 6–12 (mean 8) months before entry to the study), dilated cardiomyopathy in four patients, coronary artery disease in seven patients, hypertrophic cardiomyopathy in two patients, and hypertension in one patient. Fibrillation was idiopathic in the remaining patient. The exercise tolerance of the patients was limited only by dyspnoea or fatigue. Patients were excluded if they had had a myocardial infarction during the previous six months, had evidence of myocardial ischaemia or ventricular tachycardia on exercise testing, or had chronic lung disease. There were four patients in New York Heart Association class I, 12 patients in class II, and four in class III. Resting left ventricular fractional shortening was assessed by M mode echocardiography recorded at the mitral valve leaflet tips (with cross sectional echocardiographic control) 24 hours and 28 days after cardioversion. In those patients in whom cardioversion failed left ventricular fractional shortening was assessed as the mean of 10 consecutive cardiac cycles. All echocardiographic and Doppler studies were performed by one observer. The reproducibility for left ventricular dimensions in our laboratory is within 5% of the previous value.

All patients were in controlled atrial fibrillation with a resting heart rate less than 70 beats/minute. Drug treatment which was stable for at least a month before entry to the study included digoxin (all

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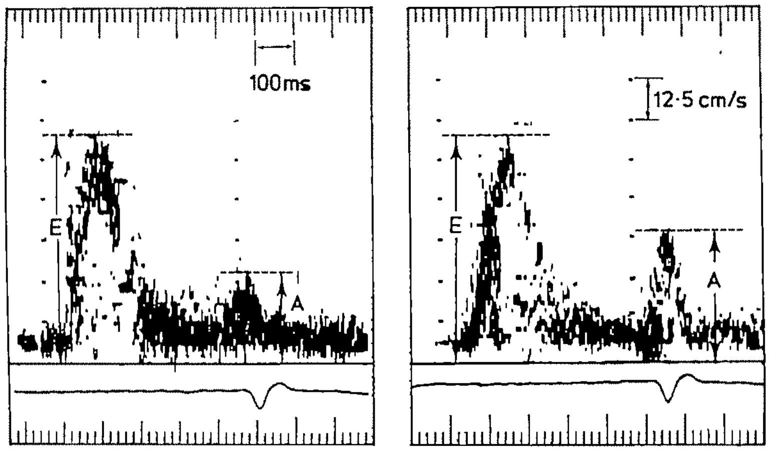
patients (median dose 0·25 mg/day), amiodarone (all patients (median dose 200 mg/day), frusemide (10 patients (mean dose 55 mg/day, range 40–80 mg/day)), amiloride (eight patients (mean dose 8 mg/day, range 5–10 mg/day)), bendrofluazide (three patients (dose of 5 mg/day)), and captopril (one patient (dose 12·5 mg three times a day). All patients were anticoagulated with warfarin for at least four weeks before cardioversion. Anaesthesia for DC cardioversion was induced with intravenous methohexitone (dose 1–2 mg/kg) injected over 30 seconds. Progressively increasing DC shocks of 100 J, 200 J, and 320 J were used until the highest energy was reached or cardioversion was achieved.

Patients were exercised three hours after a light meal and at the same time of day, according to the Bruce protocol for those in New York Heart Association class I or II or a modified Naughton protocol with stages lasting 3 minutes for those in class III.[5] The exercise protocol was not changed during the study. Patients were encouraged to exercise until they felt unable to continue; the test was stopped at the patient's request. Treadmill exercise capacity was assessed by measuring maximal oxygen consumption and anaerobic threshold with mass spectrometric analysis of mixed expired air before and on day 1 (24 hours) and day 28 after elective DC cardioversion.[5] Patients repeated practice exercise tests before entry to the study until maximal oxygen consumption differed by less than 5% on two consecutive exercise tests. In the last 12 consecutive patients left ventricular inflow velocities were measured by pulsed Doppler during quiet respiration to evaluate the relative contribution of atrial contraction to left ventricular filling. A Doppler probe was placed at the cardiac apex with patients in the left lateral position and measurements were recorded during quiet respiration. The Doppler sample was placed in the region of the mitral leaflet tips, and the positioning of the sample was guided by cross sectional echocardiography. The sampling position was adjusted to obtain the peak inflow velocities by a combination of the spectral display and Doppler audio signal. The heights of the passive filling wave (E wave) and the atrial wave (A wave) were measured over 10 consecutive cycles to avoid sampling errors caused by minor beat to beat variations, and the mean values for the height of the A wave, E wave, and the A/E ratio were calculated[6] (fig 1). The reproducibility of Doppler inflow recording was determined in five normal subjects on two successive days by two observers. All drug treatment was unaltered for the duration of the study.

Results are quoted as mean (SE). Changes in exercise capacity, heart rate, and Doppler measurements after cardioversion were analysed by the Wilcoxon matched paired rank sum test. A p value <0·05 was considered to be significant.

Results

Sinus rhythm was restored in 14 of 20 patients by 1–3



Day 1
after cardioversion

Day 28
after cardioversion

Fig 1 *Peak left ventricular inflow velocities across the mitral valve in one patient on day 1 and day 28 after DC cardioversion. The relative contribution of atrial contraction to left ventricular filling was determined by relating the mean height of the A wave to the mean height of the E wave of the velocity time curve during 10 consecutive cardiac cycles*

Table 1 *Changes in symptom limited maximum oxygen consumption, oxygen consumption at the anaerobic threshold, and heart rate before and day 1 and 28 after successful (patients 1–14) and unsuccessful (patients 15–20) DC cardioversion of atrial fibrillation to sinus rhythm*

Case No		*$\dot{V}O_2$ max (ml/kg/min)* Day 0	1	28	*Anaerobic threshold (ml/kg/min)* Day 0	1	28	*Peak exercise heart rate (beats/min)* Day 0	1	28
1	AVR	24	24	27	17	17	19	150	140	140
2	AVR	16	16	22	13	14	20	120	115	123
3	MVR	16	15	23	13	13	17	170	140	150
4	MVR	31	30	35	25	24	30	180	155	150
5	IDC	23	23	24	19	19	19	190	150	152
6	IDC	11	12	13	11	11	12	160	105	100
7	IDIO	40	40	43	18	19	22	214	160	150
8	H/T	15	15	17	14	14	15	129	101	100
9	HCM	15	16	18	NR	NR	NR	180	113	115
10	IDC	19	18	22	17	17	20	170	130	140
11	CAD	21	22	24	17	18	22	150	140	145
12	CAD	24	25	29	19	19	23	180	166	160
13	CAD	37	38	38	25	25	25	195	150	155
14	CAD	24	25	28	18	18	19	164	129	132
Mean (SE)		23(2)	23(2)	26(2)*	17(1)	18(1)	20(1)†	168(7)	135(6)‡	137(5)‡
15	MVR	31	30	33	20	19	20	180	184	185
16	IDC	22	23	21	13	14	13	150	155	145
17	HCM	21	—	18	20	NS	17	120	—	125
18	CAD	25	26	25	19	19	19	130	136	135
19	CAD	21	22	19	18	19	17	157	153	144
20	CAD	19	19	18	15	13	17	153	147	160
Mean (SE)			23(2)	24(2)	22(3)	18(1)	17(1)	17(1)	125(24)	155(8)
149(8 6)										

$\dot{V}O_2$ max, maximal oxygen consumption; AVR, after aortic valve replacement, MVR, after mitral valve replacement, IDC, idiopathic dilated cardiomyopathy; IDIO, idiopathic; H/T, hypertension; HCM, hypertrophic cardiomyopathy, CAD, coronary artery disease; NR, not reached

*p < 0 002 (compared with day 0 or 1),
†p < 0 003 (compared with day 0 or day 1),
‡p < 0·001 (compared with day 0).

(mean 1·2) DC shocks at a mean energy requirement of 130 J. Functional class as assessed by the New York Heart Association did not alter during the study.

Maximal oxygen consumption and anaerobic threshold were unchanged at day 1 and rose significantly by 16(3%) and 18(14%) respectively on day 28 (p < 0·002, <p 0·003 respectively) (table 1, figs 2 and 3). The absolute improvement in maximal oxygen consumption on day 28 was not related to left ventricular fractional shortening or to the exercise capacity (maximal oxygen consumption) before cardioversion. The percentage improvement in maximal oxygen consumption, however, correlated inversely with the value before cardioversion (r = −0·57, p < 0·01) (fig 4). Resting heart rates before cardioversion and on day 1 and 28 after cardioversion were 62(2), 69(2), and 70(3) beats/min. Peak exercise heart rate fell by day 1 (p < 0·001) but there was no significant difference between rates on days 1 and 28 after cardioversion (table 1).

In six patients cardioversion was unsuccessful. Maximal oxygen consumption and anaerobic threshold in these patients did not significantly alter during the study (table 1).

Mean left atrial size for all patients on entry to the

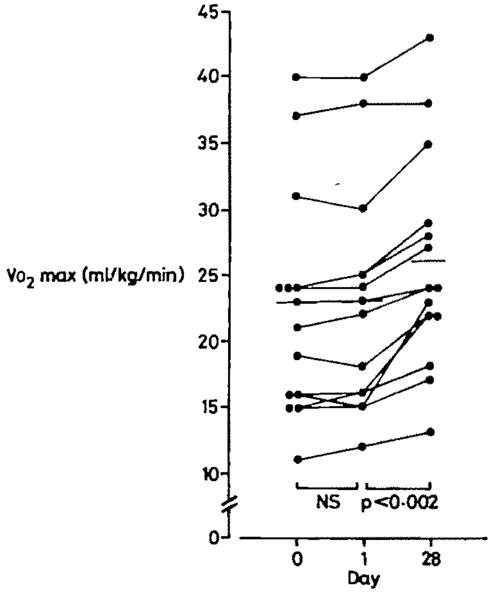


Fig 2 *Change in symptom limited maximal oxygen consumption ($\dot{V}O_2$ max) before and on day 1 and 28 after DC cardioversion of atrial fibrillation to sinus rhythm.*

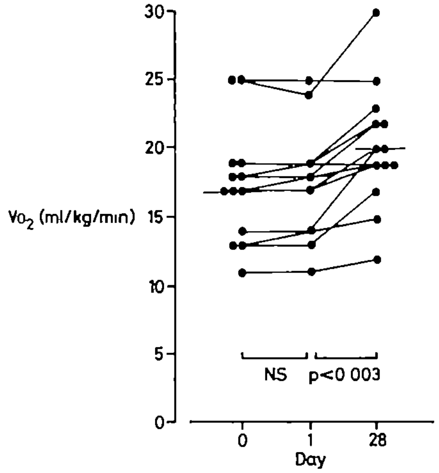


Fig 3 *Change in oxygen consumption ($\dot{V}o_2$) at the anaerobic threshold before and on day 1 and 28 after DC cardioversion of atrial fibrillation to sinus rhythm.*

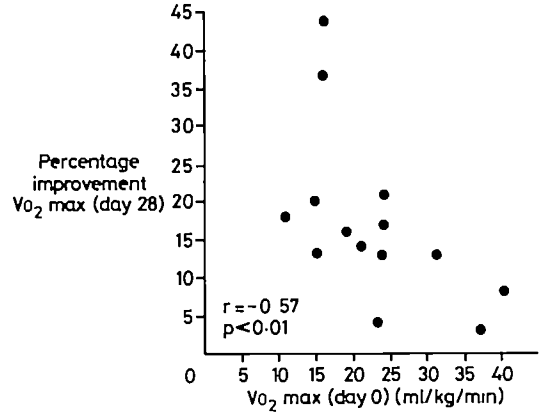


Fig 4 *Percentage improvement in symptom limited maximal oxygen consumption ($\dot{V}o_2$ max) related to maximal oxygen consumption before cardioversion (day 0).*

study was 4·3 (0·5) cm. The interobserver and intraobserver variability in normal subjects for the measurements of the height of the A and E wave and their ratio was 2–21% (mean 13%), 2–36%, (mean 15%), and 4–35% (mean 17%) respectively. Table 2 shows the Doppler results. During the Doppler studies the mean heart rates were similar on day 1 and day 28. In four patients no discernible A wave was seen on visual inspection of the Doppler tracing on day 1. Because velocities less than 12·5 cm/s could not be measured accurately the height of the A wave in these patients was assumed to be 12·5 cm/s. The mean A/E ratio was 0·32 (range 0·15–0·60) on day 1 and increased significantly in all patients to 0·80 (range 0·27–1·44) by day 28 ($p < 0·003$) (fig 5). The increase in the A/E ratio resulted solely from an increase in the size of the atrial wave (table 2). Left ventricular fractional shortening was similar in patients who underwent successful and unsuccessful cardioversion (23(7)% and 27(2)% respectively). There was no significant change in left ventricular fractional shortening between day 1 and 28 in patients in whom cardioversion was successful (23(5)% *vs* 22(5)% respectively).

Discussion

Several haemodynamic studies have demonstrated an increase in cardiac output[3, 7–10] but to our knowledge this is the first study to measure the size of the increase in exercise capacity after conversion of atrial fibrillation to sinus rhythm. Assessment of changes in respiratory gas exchange on exercise enabled us objectively to assess exercise capacity.[5] The results show that symptom limited maximum oxygen consumption and anaerobic threshold do not rise 24 hours after DC cardioversion, but a mean

Table 2 *Measurement of the height of the A wave, E wave, and A/E ratio on day 1 and 28 after successful DC cardioversion of atrial fibrillation to sinus rhythm. Doppler recordings were made at similar RR intervals on day 1 and 28*

Case No	*A wave (cm/s)*		*E wave (cm/s)*		*ECG RR interval*		*A/E ratio*	
	Day 1	*Day 28*	*Day 1*	*Day 28*	*Day 1*	*Day 28*	*Day 1*	*Day 28*
3	12·5	33·4	39·0	35·9	850	890	0·32	0·93
4	35·0	93·0	116·0	125·0	870	800	0·30	0·75
5	36·2	72·0	112·5	62·0	850	890	0·32	1·16
6	12·5	30·0	54·3	72·5	1040	1000	0·23	0·41
7	18·7	43·7	47·5	63·7	1100	1320	0·39	0·68
8	12·5	23·4	73·5	68·7	1080	1340	0·17	0·34
9	36·0	90·0	97·3	62·5	730	660	0·37	1·44
10	19·4	82·0	59·0	57·0	770	770	0·33	1·44
11	27·0	76·4	77·1	84·0	1070	1210	0·35	0·91
12	12·5	23·2	83·3	86·0	920	940	0·15	0·27
13	31·2	36·9	51·2	52·0	840	800	0·60	0·71
14	16·0	25·1	44·4	50·2	860	890	0·36	0·50
Mean (SE)	22·5(2·9)	52·4(8·0)	71·3(7·7)	68·2(6·5)	915(36)	959(63)	0·32(0·03)	0·80(0·12)
p	<0·003		NS		NS		<0·003	

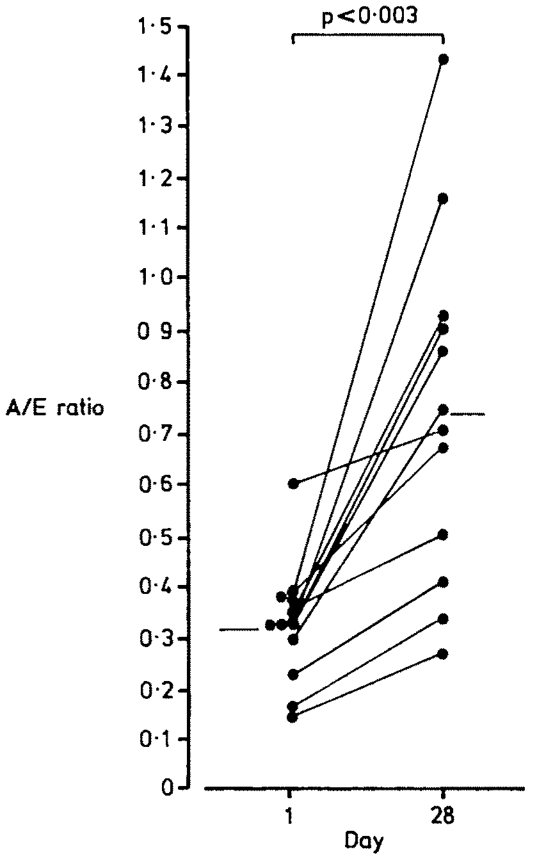


Fig 5 *Change of A/E ratio from day 1 to day 28 after DC cardioversion (10 patients)*

increase of 16% and 18% respectively is seen 28 days later. The nature of the study prevented a placebo blind trial. It is unlikely that greater encouragement by the observing doctor during the exercise tests performed after cardioversion, or increased patient familiarity with treadmill exercise, were responsible for the improvement. This is because we took care to ensure that all patients had practised on the treadmill and that their maximal oxygen consumption did not differ by > 5% on two successive tests before entry to the study. The exercise tests before and after cardioversion were performed in most instances by different doctors who were unaware of the previous exercise data. Changes in maximal oxygen consumption were associated with a corresponding change in anaerobic threshold, suggesting a true change in exercise capacity rather than an alteration in patient motivation.[5] Also the maximal oxygen consumption and anaerobic threshold were unchanged at day 28 in those patients in whom cardioversion failed.

Failure to demonstrate an improvement in exercise capacity one day after DC cardioversion could have been influenced by the after effects of general anaesthesia and of the DC shock itself. Though these possibilities cannot be excluded they are unlikely to explain the observed results. Firstly, anaesthesia lasted for less than 20 minutes and the first exercise test was performed at least 24 hours after cardioversion. Secondly, important cardiac damage, as detected by a rise in the cardiac isoenzyme of creatine kinase, did not occur with repeated elective DC shocks.[11] Thirdly, there was no difference in left ventricular fractional shortening between day 1 and 28 in the patients who underwent successful DC cardioversion in the present study. Finally, maximal oxygen consumption did not increase between day 1 and 28 in the patients in whom sinus rhythm was not restored by cardioversion.

The mechanism of the delayed improvement in exercise capacity is of interest. The reported effects of cardioversion of atrial fibrillation to sinus rhythm on haemodynamic function are inconsistent.[7–10 12] This may be because of variation in the timing and method of assessment of atrial function after cardioversion.[12–16]

We have looked in a novel way at the contribution of atrial contraction to left ventricular filling by relating the height of the A wave to the height of the E wave in the Doppler velocity time curve of flow across the mitral valve. The height of the A wave in the Doppler tracing is dependent on the pressure gradient across the mitral valve at end diastole. Because a major change in left ventricular compliance in individual patients during the study is unlikely, the height of the A wave may be taken to relate to the force of atrial contraction. The A wave was absent or small immediately after cardioversion and increased significantly at one month. In the present study peak exercise heart rates at day 1 and 28 were similar, suggesting that the improvement in exercise capacity was the result of an improvement in stroke volume that followed an increased atrial contribution to left ventricular filling.

There is an alternative explanation for the late improvement in exercise capacity after cardioversion. Cardiac output improves immediately after cardioversion because of the regularisation of rhythm that permits improved ventricular filling, but there is delayed improvement in factors which limit blood flow to the skeletal muscle. It is now firmly established that inotropic or vasodilator treatment in chronic heart failure improves cardiac output immediately, but without a corresponding improvement in exercise capacity.[17] The improvement in exercise capacity that is seen with long term treatment with angiotension converting enzyme inhibitors is limited to those patients in whom skeletal muscle blood flow increases.[18 19]

Conversion of atrial fibrillation to sinus rhythm was associated with a small (less than 1 metabolic equivalent) delayed improvement in exericse capacity. The greatest effect was seen in those patients with more severe exercise limitation. Slow return of atrial contractility and inhibition of factors limiting skeletal muscle blood flow may be responsible for the late benefit.

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Wolff-Parkinson-White syndrome: atrial fibrillation as the presenting arrhythmia

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SUMMARY Atrial fibrillation was identified as the initial arrhythmia complicating the Wolff-Parkinson-White syndrome in ten (9%) of 108 patients. Despite initially rapid ventricular responses in seven, long term survival and control of arrhythmia were excellent on medical treatment. Whereas symptom free patients with the pre-excitation syndrome who have additional underlying disease predisposing to atrial fibrillation may need detailed electrophysiological study, a more conservative approach is suitable for the typical symptom free individual.

Atrial fibrillation is a potentially serious complication of the Wolff-Parkinson-White syndrome and may degenerate into ventricular fibrillation.[1 2] When spontaneous atrial fibrillation occurs reentrant atrioventricular tachycardia has usually already been confirmed or there is a history of palpitation.[3 4]

We studied ten patients in whom atrial fibrillation was the first arrhythmia to develop. We report their clinical presentation, electrophysiological characteristics, and long term follow up.

Patients and methods

Between 1976 and 1984 electrophysiological investigation of 108 patients with the Wolff-Parkinson-White syndrome was undertaken. Ten patients were identified in whom the first episode of palpitation was shown to have been atrial fibrillation or flutter. In each case it was established that there had been no history of palpitation, dizziness, syncope, or other symptoms suggesting arrhythmia. No patient was receiving antiarrhythmic medication. The mode of clinical presentation, the appearance of the presenting electrocardiogram, age, sex, symptoms, and the presence or absence of organic heart disease were analysed. All patients underwent invasive electrophysiological study according to our protocol.[5]

A further 17 patients referred for investigation had atrial fibrillation as the presenting arrhythmia but in these there was a history suggesting previous arrhythmia.

Results

There were six male and four female patients (mean age 40 (range 16–61) years). A bimodal distribution was apparent—five were <33 and the remainder were >47 years (table 1).

CLINICAL FEATURES

When atrial fibrillation developed all had palpitation, three had near-syncope, and three had syncope. Three patients had a previous history of chronic angina pectoris and one had diabetes, hypertension, and a long history of alcoholism.

ELECTROCARDIOGRAPHIC FINDINGS

Electrocardiographic tracings recorded at the time of presentation were available in all but one patient and showed variable patterns of conduction over the accessory pathway. The range of mean ventricular responses during atrial fibrillation at initial presentation was 125–310 beats/minute. In the five patients aged 49–61 years the range of mean ventricular responses was 125–240 beats/minutes, whereas in those aged ⩽33 the range was 270–310 beats/minute. The patient in whom the initial electrocardiogram was not available (patient 10) was semiconscious at admission to hospital and required immediate direct current cardioversion for an extremely rapid and irregular ventricular rhythm.

ELECTROPHYSIOLOGICAL FINDINGS (TABLE 2)

In six patients the accessory pathway was found to be on the left free wall and in three it was posteroseptal;

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Table 1 *Summary of clinical findings in ten patients in whom atrial fibrillation was the first arrhythmia*

Patient No	*Age at presentation (y)*	*Sex*	*Symptoms*	*Other cardiac disease*	*Follow up (yr)*
1	58	M	Palpitation	Coronary heart disease	9
2	49	M	Palpitation	Coronary heart disease	6
3	33	M	Palpitation + presyncope	None	3
4	24	F	Palpitation	None	9
5	61	F	Palpitation + presyncope	Coronary heart disease	7
6	56	F	Palpitation + presyncope	None	11
7	24	M	Palpitation + syncope	None	10
8	19	M	Palpitation	None	9
9	59	M	Palpitation + syncope	Coronary heart disease, diabetes mellitus, hypertension	5
10	16	F	Palpitation + syncope	None	7

Table 2 *Electrophysiological findings in all patients*

Patient No	*Site of accessory pathway*	*AP ERP (ms)*	*Mean AF rate (beats/min)*		*SRR (ms)*	
			At EP study	*Clinically*	*At EP study*	*Clinically*
1	Left free wall	230	230	200	200	210
2	Left free wall	> SCL	140	125	520	300
3	Posteroseptal	230	245	270	210	160
4	Posteroseptal	260	173	270	220	180
5	Left free wall	280	200	180	240	230
6	Anteroseptal	290	240	260	200	180
7	Posteroseptal	230	300	305	170	180
8	Left free wall	230	300	310	200	180
9	Left free wall	290	200	240	290	190
10	Left free wall	< ARP	300	—	200	—

AP ERP, accessory pathway effective refractory period, AF, atrial fibrillation, EP, electrophysiological, SRR, shortest RR interval, ARP, atrial refractory period, SCL, sinus cycle length

it was anteroseptal in the other patient. The anterograde effective refractory period of the accessory pathway ranged from 230 to 290 ms in eight patients; in two it could not be measured owing to atrial refractoriness in one (patient 10) and because it was longer than the spontaneous sinus cycle length in the other (patient 2). All patients had inducible sustained orthodromic reentrant atrioventricular tachycardia. In two this degenerated spontaneously into atrial fibrillation while in the remainder the arrhythmia was induced by rapid atrial stimulation. Atrial fibrillation was sustained during electrophysiological study until sinus rhythm was restored, either pharmacologically or electrically in nine. Reversion to sinus rhythm was spontaneous in the tenth. The range of mean ventricular rates during atrial fibrillation was 140–300 beats/minutes with shortest RR intervals ranging from 170 ms to 520 ms.

FOLLOW UP

Patients were followed for 3–11 (median eight) years. Two have died. One (patient 2), who was treated with verapamil and quinidine, had remained free of arrhythmia until he died from carcinoma of the lung five years later. Patient 9 remained free of arrhythmia for four years and died of acute myocardial infarction that was confirmed at necropsy. Patient 8 declined treatment and continues to have reentrant atrioventricular tachycardia but not atrial fibrillation. Patient 7 takes medication erratically and has palpitation. The arrhythmia responsible has not been identified. Patient 5 is well on verapamil and quinidine; patient 4 requires varying regimens and, though he still has paroxysmal reentrant atrioventricular tachycardia, there has been no more atrial fibrillation. Three patients (cases 1, 6, and 10) are on amiodarone and have no symptoms; patient 3, also on amiodarone, has episodes of paroxysmal atrial fibrillation but with slower ventricular rates than he had originally (for example 120 *v* 270 beats/minute).

Discussion

Reetrant atrioventricular tachycardia is the most common arrhythmia in the Wolff-Parkinson-White syndrome.[6] Although atrial flutter is rare, atrial fibrillation is seen in 10–32% of patients[4] and a rapid ventricular response to this may cause not only serious haemodynamic deterioration but also ventricular fibrillation.[1 2]

Atrial fibrillation may develop for a number of reasons but the coexistence of other forms of heart disease makes it more likely.[3] Sick sinus syndrome,[7] cardiomyopathy, rheumatic heart disease,[8] and coronary heart disease can all be contributing factors but they are not necessarily prerequisites for the appearance of arrhythmia, as can be seen from our patients. Atrial or ventricular extrasystoles, reentrant atrioventricular tachycardia,[3 4] and atrial or ventricular pacing, especially in the setting of intra-atrial conduction disturbance,[4] can all precipitate atrial fibrillation.

In our study, atrial fibrillation was the initial arrhythmia in 9% of patients. In other patients with the Wolff-Parkinson-White syndrome a history of palpitation may be present and the same symptoms may be reproduced by the induction of atrial fibrillation at electrophysiological study. It may, therefore, be the first arrhythmia in a higher proportion of patients with pre-excitation but not be identified as such.

In older patients, for reasons that are unclear, the ventricular response was slower. The higher incidence of coexisting disease may, however, have provided the mechanism for initiation of the arrhythmia.

In younger patients, extremely rapid ventricular rates were seen and one required direct current cardioversion. In a retrospective study Klein *et al* showed that rapid ventricular responses to atrial fibrillation were associated with ventricular fibrillation.[2] The degree to which induced atrial fibrillation is predictive of ventricular fibrillation has not, however, been prospectively evaluated. A rapid ventricular response to atrial fibrillation may be a highly sensitive marker for the development of ventricular fibrillation but it may be non-specific and other factors are known to have a role including digitalis[1] or other drugs.[9] Despite this, our median follow up over eight years suggests that such patients have a good medium term surival when they are medically managed. Furthermore, treatment was successful in preventing atrial fibrillation and in controlling the ventricular response if it recurred. Surgical ablation was advocated in only one patient but he declined it. He now has fewer and milder attacks. The other patients have opted for medical management despite the satisfactory long term results of operation.[10]

These findings counterbalance those of Milstein *et al* who found that 17% of symptom free patients with the Wolff-Parkinson-White pattern had "potentially lethal ventricular rates during induced atrial fibrillation",[11] a figure which is clearly in excess of sudden death rates in this syndrome.

The role of electrophysiological study in the symptom free patient with resting pre-excitation remains unclear.[12] The risk of rapidly conducted atrial fibrillation is small and although a previous history of reentrant tachycardia has been thought to be an important risk factor for the development of atrial fibrillation our results indicate that such a history may not always be present.

It has been suggested that electrophysiological study may be important even in symptom free individuals[11] but identification of those at high risk of development of atrial fibrillation, such as those with mitral valve disease or Ebstein's anomaly, may allow more appropriate selection of patients in such studies. The presence of rapid ventricular rates during induced atrial fibrillation in many patients who are usually symptom free[11] emphasises the necessity of interpreting these values in the context of other predictors of high risk. A prospective study of pooled electrophysiological and epidemiological data from several centres may help to elucidate the natural history of atrial fibrillation in the Wolff-Parkinson-White syndrome and its relation to sudden death.

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Distribution of age at death in children with congenital heart disease who died before the age of 15

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SUMMARY In the 27 years from 1952 to 1979 (before the introduction of advanced cardiac surgery) all children in Central Bohemia (population 1·2 million) who died before the age of 15 were examined at necropsy. Period death rates at various ages were calculated in those with congenital heart disease. Nearly all the deaths (848, 89·6%) occurred in the first year. Forty three (44% of survivors) died in the second year and 17 (31% of survivors) died between the second and fifth years. Over half (20) of the survivors died between the fifth and tenth years. Nearly half (44·2%) of those born with congenital heart disease who died before the age of 15 died in the first four weeks. About a third (29·1%) died in the first week and period death rates were 9·7%, 7·6%, and 5·7% for the second, third, and fourth weeks respectively. In neonates death rates were highest in those with hypoplastic left heart syndrome (89·2%), coarctation of the aorta (66·7%), truncus arteriosus (61·8%), double outlet right ventricle (57·1%), and pulmonary atresia (56·3%).

A necropsy was performed on all children who died in Central Bohemia (population 1·2 million) before the age of 15 in a 27 year period from 1952 to 1979. We reviewed the data on children with congenital heart disease, which were collected before the introduction of advanced cardiac surgery. The distribution of the congenital heart malformations found in the dead children has been reported elsewhere.[1]

In the present study we examine the distribution of the age at death in children who died before the age of 15 and in whom various congenital heart defects were found at necropsy.

Patients and methods

Central Bohemia, the ~~area around Prague, has a~~ population of 1·2 million and has industrial and agricultural regions. The largest town has 70 000 inhabitants. During the 27 years of the study there was little movement of population into or out of the area. All children who died from 1952 to 1979, either at home or in a hospital, before they were 15 were examined at necropsy. The necropsy was done or supervised by DB. Congenital heart disease was found in 946 liveborn children. The necropsy protocols were analysed carefully and some cases were reclassified to comply with the contemporary nomenclature.[1] In a complex congenital heart disease the malformation that determined a haemodynamic function was regarded as dominant.

Before 1979 only children with ductus arteriosus were treated by operation. Three children in our study died after operation for closure of the ductus arteriosus. In 1952 shunt operations were introduced for the treatment of older children, and from 1968 they were used to treat infants. Fourteen of the deaths in our study occurred in children with a systemic to pulmonary anastomoses. Banding of the pulmonary artery was first performed in 1964 and all eight children who died after the banding are included in this study. Until 1970 coarctation of the aorta was treated surgically only in children over three years of age. Twelve children died after open heart surgery for tetralogy of Fallot. There were three deaths after operation for ventricular septal defect and three after correction of atrial septal defect and pulmonary stenosis. Balloon atrial septostomy was introduced in 1967; this was the technique that had been used in 14 patients with transposition of the great arteries, in three with pulmonary atresia, and in

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Table 1 *Period death rates in children with various congenital heart diseases who died before the age of 15 in Central Bohemia*

Heart disease	*No*	*Period of life (years)* *0–1 (%)*	*1–2 (%)*	*2–5 (%)*	*5–10 (%)*	*10–15 (%)*
Aortic stenosis	26	76 9	33 3	00 0	25 0	100
Atrial septal defect	47	78 7	70 0	66 7	00 0	100
Atrioventricular septal defect	60	93·3	75 0	100		
Coarctation of the aorta	57	96 5	00 0	00 0	50 0	100
Double outlet right ventricle	42	92 9	33 3	00 0	50 0	100
Hypoplastic left heart syndrome	102	100				
Ductus arteriosus	34	88 2	50 0	00 0	50 0	100
Pulmonary atresia	48	93 8	66 7	00 0	00 0	100
Pulmonary stenosis	10	70 0	33 3	00 0	100	
Single ventricle	32	87 5	75 0	100		
Tetralogy of Fallot	69	53 6	31·3	18 2	61 1	100
Total anomalous pulmonary venous connection	24	95 8	100			
Transposition of the great arteries	100	99 0	100			
Tricuspid atresia	14	71·4	100			
Truncus arteriosus	34	94 1	50 0	100		
Ventricular septal defect	203	91 1	27 8	61 5	60 0	100
Others	44	97 7	100			
All	946	89 6	44 0	31 0	54 0	100

one with supracardiac total anomalous pulmonary venous connection.

We calculated the period death rates for various age groups—the number of deaths in a given period calculated as a percentage of those who were alive at the start of the period.

Results

AGE AT DEATH IN CHILDREN WITH CONGENITAL HEART DISEASE WHO DIED BEFORE THE AGE OF 15

All heart diseases

Nearly all the deaths (848, 89·6%) occurred in the first year of life (table 1). Nearly half (43, 44%) of those who survived the first year died in the second year and a third (17, 31%) of those surviving the second year died before they were six years old. Over half (20, 54%) the survivors died between the fifth and tenth years of life. The remainder died before reaching the age of 15.

Nearly half (44%) of those born with congenital heart disease died in the first four weeks (table 2). A fifth of the survivors of the neonatal period died in the second month. The next highest period death rate (19·9%) was in the fourth month. Period death rates for the third month and between the fifth and seventh months ranged from 16·3% to 17·9%. Period death rates were lower from the seventh month onwards.

In total, 29·1% of the children with heart disease

Table 2 *Period death rates in infants with various congenital heart diseases*

Heart disease	*No*	*Period of life (months)* *0–1 (%)*	*1–2 (%)*	*2–3 (%)*	*3–4 (%)*	*4–5 (%)*	*5–6 (%)*	*6–7 (%)*	*7–8 (%)*	*8–9 (%)*	*9–10 (%)*	*10–11 (%)*	*11- (%*
Aortic stenosis	26	42·3	20 0	16 7	20 0	12 5	00 0	00 0	14 3	00 0	00·0	00 0	00
Atrial septal defect	47	29·8	12 1	13 8	4 0	29 2	11 8	13 3	77 0	8 3	00·0	00 0	9
Atrioventricular septal defect	60	16 7	8 0	15 2	23 1	20 0	25·0	22 2	14·3	33 3	25·0	00·0	33
Coarctation of the aorta	57	66 7	21·1	13·3	23 0	20 0	12 5	28 6	00 0	20 0	50 0	00·0	00
Double outlet right ventricle	42	57 1	17 6	35 7	44 4	25 0	00 0	25 0	00 0	00 0	00 0	00 0	00
Hypoplastic left heart syndrome	102	89 2	54 5	00 0	40 0	00 0	33 3	00 0	50 0	00·0	100		
Ductus arteriosus	34	11·8	23·3	27 3	37 5	10 0	10·5	28 6	20 0	00 0	00 0	00 0	00
Pulmonary atresia	48	56 3	28 6	20 0	16 7	50 0	20 0	25 0	00 0	00 0	00·0	00·0	00
Pulmonary stenosis	10	30 0	00 0	00 0	14·3	16 7	00 0	00 0	20·0	25·0	00·0	00 0	00
Single ventricle	32	18 8	19 2	19 0	5 9	12 5	28 0	10 0	11 1	00 0	37 5	20 0	00
Tetralogy of Fallot	69	23 2	11 3	2 1	4 4	9 1	5·0	2 6	8 1	5 9	00·0	00 0	00
Total anomalous pulmonary venous connection	24	41 7	30 8	44·4	40 0	00 0	00 0	33 3	00 0	00 0	50 0	00·0	00
Transposition of the great arteries	100	47 0	43 4	26 7	22·7	11 8	20 0	33 3	12 5	42·9	00 0	00 0	75
Tricuspid atresia	14	21 4	18 2	11 1	12 5	00 0	14 3	16 7	20·0	00·0	00 0	00 0	00
Truncus arteriosus	34	61 8	30·8	11 1	37·5	00 0	25 0	00 0	00 0	00·0	00 0	00 0	33
Ventricular septal defect	203	36 9	18 0	21·0	25 3	22 6	20·4	25 6	10·3	15 3	13 6	34·5	00
Others	44	40 9	19 2	33·3	21·4	9 1	20·0	25 0	00·0	33·3	25 0	33·3	50
All	946	44 2	20 6	17·9	19 9	17 2	16 3	16 8	10·1	12 7	10 5	2 7	7

Table 3 *Period death rates in neonates (1 to 4 weeks old) with various congenital heart diseases*

		Period of life (weeks)			
Heart disease	*No*	*0–1 (%)*	*1–2 (%)*	*2–3 (%)*	*3–4 (%)*
Aortic stenosis	26	26·9	15·8	6·3	00·0
Atrial septal defect	47	17·0	5·1	5·4	5·7
Atrioventricular septal defect	60	6·7	3·6	7·4	00·0
Coarctation of the aorta	57	35·1	18·9	26·6	13·6
Double outlet right ventricle	42	75·0	25·0	00·0	00·0
Hypoplastic left heart syndrome	102	68·6	34·4	23·8	31·3
Ductus arteriosus	34	2·9	00·0	00·0	9·1
Pulmonary atresia	46	58·3	14·3	12·5	00·0
Pulmonary stenosis	10	30·0	00·0	00·0	00·0
Single ventricle	32	3·1	6·5	6·9	3·7
Tetralogy of Fallot	69	17·4	1·8	1·8	3·6
Total anomalous pulmonary venous connection	24	4·2	8·7	23·8	13·3
Transposition of the great arteries	100	27·0	12·3	11·1	7·0
Tricuspid atresia	14	7·1	7·7	00·0	8·3
Truncus arteriosus	34	44·1	15·8	6·3	13·3
Ventricular septal defect	203	73·9	6·0	4·3	5·2
Others	44	31·8	10·0	3·7	00·0
All	946	29·1	9·7	7·6	5·7

that we studied were dead by the end of the first week. The period death rates for the second, third, and fourth weeks were 9·7%, 7·6%, and 5·7% respectively.

Heart disease categories

In neonates the highest death rates (89·2%) occurred in those with hypoplastic left heart syndrome (table 2). Coarctation of the aorta, truncus arteriosus, double outlet right ventricle, and pulmonary atresia were associated with death rates of >50%. Death rates were lower in those with ductus arteriosus, atrioventricular septal defect, and single ventricle (table 3).

Period death rates in the second month of life also showed the highest rates for hypoplastic left heart (table 2); but coarctation of the aorta fell from the second most highest rate to the seventh. It was replaced in second place by transposition of the great arteries. The third highest period death rate (30·8%) for those who survived the first month of life was found in those with total anomalous pulmonary venous connection and truncus arteriosus. Pulmonary atresia remained in fifth position. No child with isolated pulmonary stenosis died in the second month of life. In the second month, period death rates for atrioventricular septal defect, tetralogy of Fallot, and atrial septal defect were very low.

Nearly all the deaths occurred in the first year after birth, but there was variation in period death rates for different heart diseases (table 1). All children with the hypoplastic left heart syndrome died during this period, as did >90% of those with transposition of the great arteries, coarctation of the aorta, total anomalous pulmonary venous connection, truncus arteriosus, pulmonary atresia, atrioventricular septal defect, double outlet right ventricle, and ventricular septal defect.

DEATH RATES ASSOCIATED WITH DIFFERENT HEART DISEASES

In patients in whom ventricular septal defect was diagnosed at necropsy the highest period death rate occurred in the first month (table 2). In the second month the death rate was halved and for the third to seventh months of age period death rates ranged from 20·4 to 25·6%. After this period period death rates were low, except in the eleventh month. In those who survived infancy the period death rate was lowest (27·8%) in the second year of life (table 1).

Most (89·2%) children with the hypoplastic left heart syndrome did not survive the first month of life (table 2), and period death rates remained high throughout infancy. The remainder of those dying before they were 15 died in the tenth month of life.

Forty seven per cent of children born with transposition of the great arteries who died before they reached 15 died in the neonatal period (table 2). The period death rate was high in the first week (table 3). The period death rate in the second month was only slightly lower (43·4%) and it became lower during the next three months. The period death rate was highest in the patients who survived till the end of the first year. The rest of the patients died in the second year of life (see table 1).

Those who died with tetralogy of Fallot had the lowest (53·6%) period death rate in infancy of all the categories of heart disease. Later in childhood period death rates in children with this defect became higher (table 1).

The period death rate in children with atrioventricular septal defects was one of the lowest in the first two months. This increased from the fourth month and the last patients died between the second and fifth years of life (table 1).

In the first year of life the period death rate (96·5%) in those with coarctation of the aorta was the third highest for any disease category (table 1). In neonates coarctation of the aorta had the second highest period death rate (table 2). During the first to the eighth months it varied between 12·5 and 28·6%. No patient died in the period from the eleventh month to the fifth year of age.

More than half of patients (58·3%) with pulmonary atresia died in the first postnatal week (table 3). Period death rates were high in the first seven months of life. In total 93·8% of those with fatal pulmonary atresia died in infancy. Those who survived the first two years of life tended to survive until they were 15.

Period death rates in children with atrial septal defect were 78·7% in the first year and 70·0 and 66·7% in the two succeeding periods (1–2 and 2–5 years). In infancy the period death rate was lowest in the later months.

Most (92·9%) children with double outlet right ventricle died in the first seven months of life (tables 1 and 2). The period death rate in the second year of life dropped to 33·3%.

For children with truncus arteriosus the period death rate was highest (94·1%) in the first year of life, especially in the first four months (tables 1 and 2). The last patient died before the age of five.

All patients who died in childhood with total anomalous pulmonary venous connection or tricuspid atresia died in the first two years of life (table 1). All those with a single ventricle were dead before the age of five. Period death rates in those with ductus arteriosus were high early in infancy and very low in the last four months of infancy and between the second and fifth years of life. Period death rates for aortic stenosis were highest in the first five months.

Discussion

We studied a group of children with heart disease who died before the age of 15. Our data on the mortality of children with a heart disease and the incidence of congenital heart disease show that such cases make up about one third of all children born with heart disease.

Table 4 compares our results with those of other studies of mortality in children with a congenital heart disease.[2-8] The period death rate in the first week after birth ranges from 27% to 54%. Our figures for the first week and first month are higher than those of Kerrebijn[6] but lower than those of all other reports. At the end of the first year of life the period death rate in our series was within the reported range but it was higher than the mean period death rate of 84% for all reported studies. Our series has the advantage of being more than four times larger than the largest series reported so far and of giving complete coverage of all deaths, both in hospital and at home. We also had systematic coverage of total child deaths, which excludes various selection bias of other studies.

The duration of the study (27 years) eliminates possible year to year variations in the period death rates and disease specific death rates. The decline in infant mortality in Central Bohemia from 30 per 1000 of liveborn children in 1952 to 15·7/1000 in 1979 may have influenced our results. There was not a proportional decrease in the mortality of children with congenital heart disease. On the contrary, the proportion of deaths from congenital heart disease increased from 4·7% of total deaths in 1952 to 7·8% in the last five years of the study.

We studied a period before surgical treatment could have had an appreciable effect on death rates. Only period death rates in those with ductus arteriosus were likely to have been affected by surgical treatment. Nevertheless, operations for ductus arteriosus were only done occasionally in infancy when the period death rate was highest and so such interventions are unlikely to have significantly changed the results. Similarly, the anastomosing operations for tetralogy of Fallot, which were done only in older children until 1968 and in a very limited number of patients below the age of four years in the

Table 4 *Period death rates (%) in children with congenital heart disease reported in other series*

Authors	*Reference*	*No of cases*	*Age* *1 week*	*1 month*	*1 year*	*15 year*
Carlgren	2	145	36	56	86	100
Feldt *et al*	3	81	54	70	92	100
Gardiner and Keith	4	29	—	55	83	100
Hoffman and Christianson	5	43	—	51	—	100
Kerrebijn	6	15	27	40	80	100
Mustacchi *et al*	7	171	40	49	82	100
Renwick *et al*	8	206	—	—	83	100
Šamánek	This study	946	29	44	90	100

last years of study, could not have influenced the results markedly. A balloon atrial septostomy can postpone but not change the unfavourable outcome of transposition of the great arteries, and period death rates before and after 1967 (when the septostomy was introduced) did not differ significantly.

The finding of heart disease at necropsy does not necessarily mean that it, rather than another lethal disease, was the cause of death. In an earlier report we found that heart disease could have been responsible for death in only 45% of those neonates in whom a heart malformation was found at necropsy.[9]

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Case reports

His bundle haemorrhage and external cardiac massage: histopathological findings

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SUMMARY Histological examination showed acute haemorrhage of the bifurcating His bundle and of the left bundle branch in a 35 year old man who died after being given external cardiac massage for cardiac arrest. "Hammering" of the ventricular septum crest against the central fibrous skeleton of the heart by compression of the sternum was believed to have caused the haematoma of the junctional tissue.

There is a risk of injury to the heart during external cardiac massage.[1] Cardiac rupture (particularly of the right atrium), and epicardial, endocardial, and/or intramyocardial haemorrhage have been reported,[1] as a consequence of the pressures that must be applied during this emergency manoeuvre[2] (fig 1). But the possibility of lesions of the specialised junctional tissue has not been investigated.

We report the histopathological findings in the

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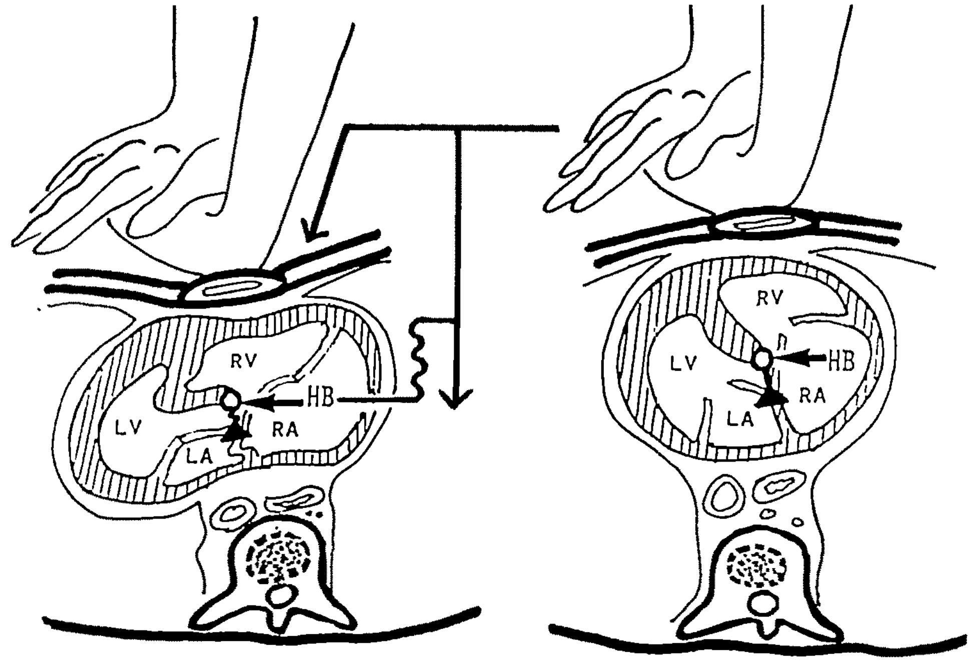

Fig 1 *The mechanics of external cardiac massage. The ventricular septum is in parallel with the axis of sternal compression (left) and relaxation (right) and is crushed repeatedly, thereby hammering the bifurcating His bundle against the heart's fibrous skeleton (black triangle). HB, His bundle; LA and LV, left atrium and ventricle; RA and RV, right atrium and ventricle.*

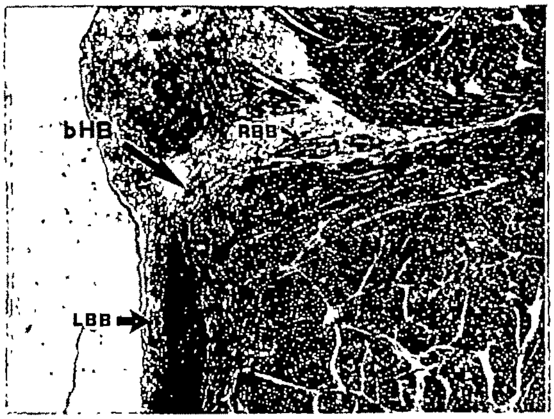

Fig 2 *Haematoma of the proximal left bundle branch, from the hisian bifurcation downwards; the root of the right bundle branch is intramural. Azan stain, original magnification × 25. bHB, bifurcating His bundle; LBB and RBB, left and right bundle branch.*

conduction system of a patient who did not survive cardiac arrest, despite correctly applied closed chest cardiac massage.

Case report

A 35 year old man, with no history of heart disease suddenly presented with life-threatening shock; resuscitation attempts, including external cardiac massage, were continued until the patient died of a cardiac arrest. At necropsy an acute anterolateral myocardial infarction was found. Histological examination of the conduction system[3] showed a recent subendocardial septal haematoma of the proximal left bundle branch and the hisian bifurcation; the root of the right bundle branch was intramural (fig 2).

Discussion

Did the His bundle haemorrhage occur during life or immediately after death? Efforts at emergency resuscitation usually continue until after the patient has died. Because reliable electrocardiograms cannot be obtained during cardiac massage the exact time of death cannot be determined. Moreover, raised intracranial pressure and hypoxia can cause spotty haemorrhagic effusions in the heart of people who die of cardiorespiratory arrest, particularly those on anticoagulants.

None the less, whatever other factors may have been responsible for findings in other cases, we believe that in our patient the junctional haematoma was caused by injury during attempted resuscitation.

During classic closed chest cardiac massage (fig 1) the heart is squeezed between the sternum and the spinal column; considerable pressure must be applied by the operator to achieve adequate pumping of the ventricular chambers. Ejection of blood usually provides some compliance to protect the free walls of the ventricles from injury. But the stiff ventricular septum, which lies along the axis of the piston action, is crushed and bent during each sternal compression (fig 1); in particular, the bifurcation of the His bundle, which straddles the septal crest, is hammered against the anvil of the central cardiac skeleton (fibrous body/aortoventricular membrane[4]). Because it is the target of heavy, repeated impacts this site is at increased risk of traumatic bleeding (fig 2).

We are not questioning the rationale of closed-chest massage; however, we believe that whenever the heart is crushed by accident or during resuscitation, the potential effect on the conduction system must be remembered.

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Coronary angioplasty in pregnancy

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SUMMARY Myocardial infarction is rare in pregnancy. A 30 year old white primigravida had an anterior infarct at 20 weeks' gestation, which was followed by troublesome angina. Coronary angiography showed a tight stenosis of the left anterior descending coronary artery. This was treated successfully by percutaneous transluminal coronary angioplasty.

Case report

A 30 year old white woman presented at 20 weeks' gestation in her first pregnancy with paraesthesiae and severe pain in her left arm and hand. This was followed by a dull feeling of intense retrosternal pressure radiating down both arms, which was associated with profuse sweating, nausea, and vomiting. There was no previous medical or drug history.

The patient had smoked 30 cigarettes a day for fourteen years. Her father and paternal uncle had died after myocardial infarction aged 39 and 40 years respectively. There were no other associated risk factors for myocardial infarction.

The patient was admitted from home directly to the coronary care unit of her local hospital. The first electrocardiogram showed unequivocal ST elevation in leads I and V2–V6. Because the symptoms persisted she was given intravenous diamorphine. While she was being examined cardiac ventricular fibrillation occurred. Cardiopulmonary resuscitation was performed and intravenous lignocaine was administered; four direct current shocks were required to restore sinus rhythm.

Four days later further typical ischaemic chest pain occurred which did not settle despite intravenous infusion of isosorbide dinitrate. She was also treated with oral nifedipine 20 mg twice a day, atenolol 100 mg twice a day, slow release isosorbide dinitrate 20 mg twice a day, diazepam 2 mg three times a day, and potassium supplements. Urgent transfer to a regional cardiac centre was arranged.

On arrival at the centre a 12 lead electrocardiogram showed diminished R waves in leads V1–V4, normal ST segments, and T wave inversion in lead V1 only. Ultrasonography showed a normal fetus. The gestational age was estimated to be 20·5 weeks by measurement of the biparietal diameter. Coronary angiography, performed from a right brachial approach by the Sones' technique, showed a single pronounced proximal stenosis of the left anterior descending coronary artery (fig 1a) and some irregularity of the posterior descending branch of the right coronary artery. The left main stem and circumflex arteries were normal. The left ventriculogram showed an akinetic anterior wall (fig 2a). During the procedure the fetus was protected by positioning lead aprons behind and over the anterior wall and flanks of the patient's abdomen. The radiographic screening time was kept as short as possible. Thermoluminescent dosimetry measurements of the radiation dose received by the patient's skin showed a maximum fetal dose of <0·55 mSv. We assumed that a completed myocardial infarct had occurred. The patient's symptoms settled and a ten day postinfarct submaximal exercise test (equivalent to completing stage 1 of the Bruce protocol) was well tolerated. There were no cardiac symptoms or ST changes and there was a satisfactory rise in blood pressure. The test was performed on the same oral medication as that given before transfer to the regional centre, and she remained on this combination on discharge.

Nine days after discharge she had further central chest pain. The patient was immediately admitted to the regional cardiac centre. The electrocardiogram showed deep T wave inversion in leads I, aVL, and V2–V6. Treatment with intravenous isosorbide dinitrate was started and the patient was anticoagulated with a constant infusion of intravenous heparin. The patient's chest pain continued despite full medical treatment.

Percutaneous transluminal angioplasty of the tight stenosis of the left anterior descending artery was performed via a right femoral approach with a left coronary guide catheter (USCI), a 0·018 inch high torque floppy guide wire (ACS), and a 3 mm dilata-

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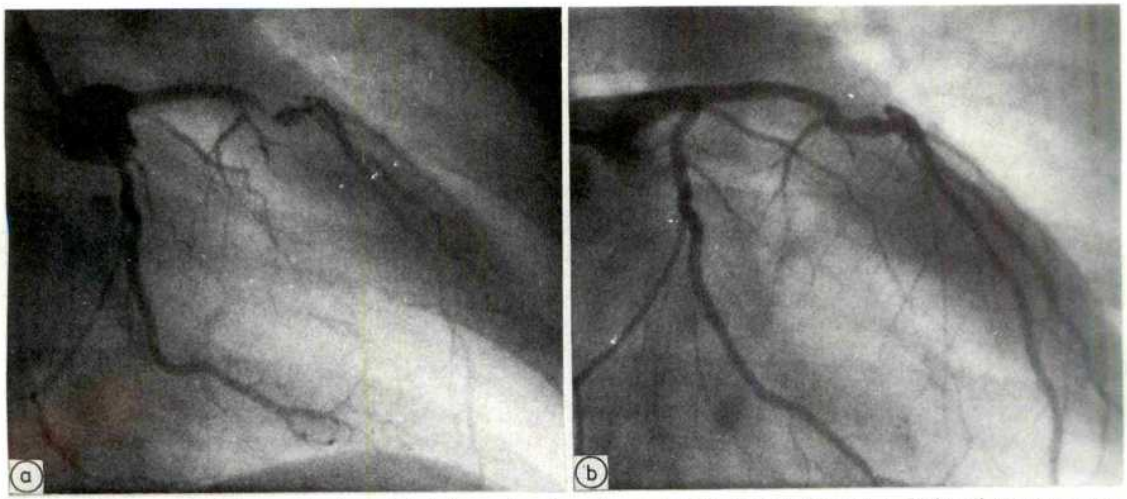

Fig 1 *Right anterior oblique projections of the left anterior descending coronary artery before (a) and after (b) percutaneous transluminal coronary angioplasty.*

tion catheter (ACS). Four inflations at 808 kPa pressure were made each for 60 seconds with good result (fig 1b). T wave changes were seen during the procedure but no pain was experienced. Screening time was again kept to a minimum and the fetus was shielded as for the earlier angiogram. Thermoluminescent dosimetry measurements indicated that the maximum radiation dose to the fetus was <0·7 mSv. A constant intravenous heparin infusion was continued for 24 hours. After angioplasty the patient was treated with dipyridamole 100 mg three times a day, aspirin 75 mg once a day, diltiazem 60 mg three times a day, and one Transiderm-Nitro patch daily (releasing 5 mg of glyceryl trinitrate).

Two days after angioplasty the patient had an exercise test, performed according to a modified Bruce protocol; she exercised to an equivalent of one minute into stage 4 of the Bruce protocol and did not experience angina. There were no ST changes and blood pressure was well maintained.

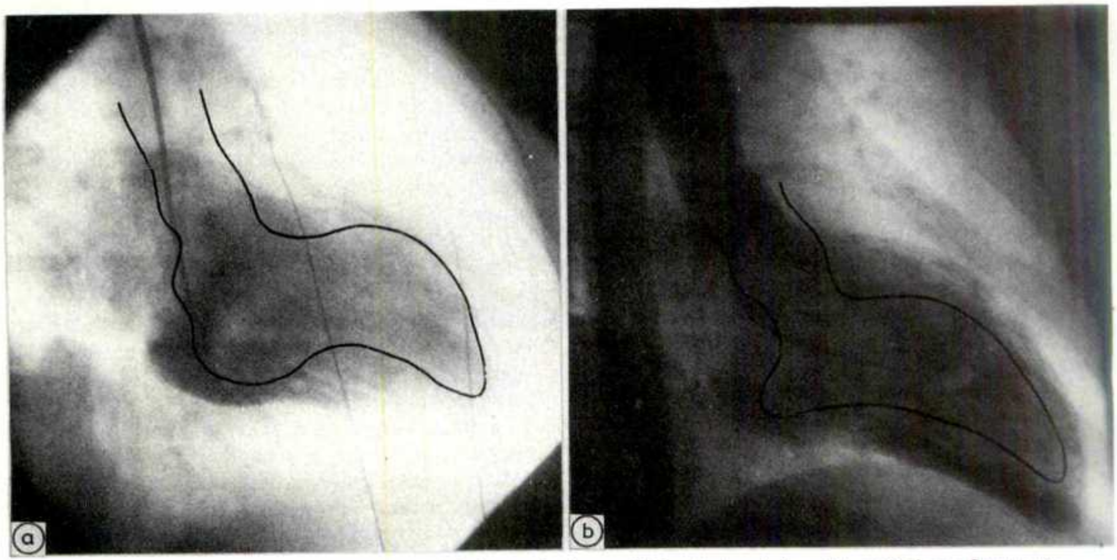

Fig 2 *(a) Right anterior oblique projection of the left ventriculogram before (a) and after (b) angioplasty. Image was obtained in diastole with systolic outline superimposed. (a) Shows anterior akinesia and (b) shows improved anterior wall motion. (b) Right anterior oblique projection of the left ventriculogram in diastole with systolic outline superimposed.*

The patient was discharged home and was reviewed monthly throughout the remainder of her pregnancy, during which she was free from angina. She acted on advice to give up smoking. The electrocardiographic changes gradually reverted and the electrocardiogram was normal at delivery. At 36 weeks' gestation the fetus was found to be breech presentation. At 38 weeks an elective lower segment caesarean section was carried out under general anaesthesia. A healthy boy weighing 3·46 kg was delivered. Three months after the angioplasty, follow up angiography was performed at the patient's request. This showed improved anterior wall motion (fig 2b). The site of dilatation was satisfactory. After the procedure the patient used a Transiderm-Nitro patch daily for six months, remained on diltiazem and aspirin for eighteen months, and is currently still taking dipyridamole. Two years after the angioplasty both mother and child remain well. There is no evidence of diabetes mellitus or hyperlipoproteinaemia.

Discussion

We believe this to be the first report of a case of percutaneous transluminal coronary angioplasty in pregnancy. The indication for treatment of the tight stenosis of the left anterior descending coronary artery was the occurrence of angina resistant to medical treatment two weeks after an anterior myocardial infarction.

Myocardial infarction in pregnancy is rare, with a frequency which is thought to be of the order of 1 in 10 000 deliveries.[1] The overall mortality is probably similar to that of myocardial infarction in non-pregnant patients. It has been suggested that mortality is related to gestational age at infarction, being higher in late pregnancy when vascular stresses are at their greatest.[2] Successful resuscitation from ventricular fibrillation has been reported, with maternal and fetal survival.[2 3]

The risk factors for myocardial infarction in young women include smoking, hypertension, diabetes, familial hyperlipoproteinaemia, and use of oral contraceptives.[4 5] Of these, cigarette smoking is the most important identified risk factor.[6]

The choice of drug treatment for pregnant patients with symptomatic coronary artery disease must take into account any possible adverse effects of the drug on the fetus. There is no absolute contraindication to the use of a β blocker in pregnancy; this form of treatment has been used safely in hypertensive pregnant patients.[7] Early reports suggesting association with growth retardation, acute fetal distress in labour, hypoglycaemia in the newborn, and a high perinatal mortality[8-10] were not confirmed by subsequent controlled studies.[11] Although β blockers are excreted in small amounts in breast milk, there is no evidence that this transfer is of any importance, at least in patients taking atenolol.[12] There is no evidence that nitrates cause fetal abnormalities.[13] All calcium antagonists cross the placenta and can inhibit uterine contractions; nifedipine and verapamil have been used as tocolytic agents in cases of premature labour and there is no evidence that these two drugs cause fetal malformations.[14 15] Diltiazem, however, remains a suspected human teratogen.[16]

In survivors of uncomplicated myocardial infarction in pregnancy, the method of delivery should depend on obstetric factors only. Survey of the reported cases suggests that management of the actual delivery is based more on belief than knowledge.[1] Some cases of myocardial infarction in pregnancy are associated with normal angiographic appearances of the coronary arteries.[17] In view of the possibility of coronary artery spasm, it seems wise not to use ergometrine immediately after delivery in survivors of myocardial infarction in pregnancy. Similarly, oxytocin infusion should be avoided if possible.[2]

Our patient continued to have angina after myocardial infarction. It rapidly became unstable despite further treatment and it was thought that she required intervention for the known stenosis of the left anterior descending coronary artery. The earliest reports of cardiac operation (closed mitral commissurotomy) during pregnancy appeared in 1952[18]; since then several hundred cases of commissurotomy have been reported without the need for cardiopulmonary bypass. The maternal death rate was $<2\%$ and fetal loss was 7·5–9%. Cardiopulmonary bypass during pregnancy has been reported in less than 100 cases, and the mortality results for mother and fetus have improved with time. Maternal mortality was about 4% but it is now no different from that of the overall population undergoing cardiopulmonary bypass.[18] Fetal loss has been reduced from an early rate of 30%, but it is still considerable (about 10%). There is only one report, however, of coronary artery bypass surgery during pregnancy[19]—in a 36 year old patient with severe angina and a 90% stenosis of the left main coronary artery. The patient was 12–14 weeks' pregnant and later delivered a normal child. This was her fifth pregnancy.

Coronary angioplasty is an attractive alternative especially in a case of essentially single vessel disease with a proximal lesion in the left anterior descending coronary artery. Although there is a small risk of complications that can lead to the need for urgent operation, angioplasty does not require a general anaesthetic and cardiopulmonary bypass. The options were put to our patient who consented to the procedure.

We took care to reduce fetal irradiation by limiting the exposure time and protecting the fetus with lead shields. The maximum fetal dose was estimated to be less than 0·7 mSv during the angioplasty and less than 0·55 mSv at the time of the initial cardiac catheterisation. This is well within the limits of acceptable risk to the fetus. The current consensus of expert opinion in the United States suggests that there is no reason for concern if the dose to the embryo is < 10 mSv at any stage of the pregnancy. With exposure of less than 10 mSv, current evidence suggests that the risk of adverse effects (teratogenesis, carcinogenesis, and prenatal death) is small compared with the spontaneous incidence (4–6%) of congenital abnormalities in liveborn infants with no history of irradiation. If the dose to the embryo was in the 10–100 mSv range, radiation risk alone is not grounds for recommending therapeutic abortion. Only if the dose to the embryo was > 100 mSv should therapeutic abortion be recommended on grounds of *x* ray exposure alone.[20] For comparison, the gonadal dose received with a routine abdominal radiograph or an intravenous urogram is 1 mSv and 4 mSv respectively.

There have been no studies to determine the optimal drug regimen after percutaneous transluminal coronary angioplasty nor is it known how long such a regimen is required. We routinely give heparin for 18–24 hours after angioplasty, particularly in patients with unstable angina, and maintain the patient on vasodilator (nitrates, calcium antagonists, or both) and antiplatelet drugs. β Blockers are usually avoided. Administration of heparin during and after the angioplasty was considered to be relatively safe because heparin does not cross the placenta.[21] Warfarin and other coumarin derivatives are teratogenic and should be avoided in the first trimester of pregnancy[21-23] and if they are used later they should be stopped before labour to prevent excessive blood loss. Studies of an association between the ingestion of aspirin and the development of fetal malformations are inconclusive[24-26]; any possible association probably requires the ingestion of large doses of aspirin, as does the promotion of premature vasoconstriction of the ductus arteriosus, which can lead to increased fetal pulmonary artery pressure and, during long term treatment, disturbance in pulmonary vascular development. In our case we prescribed a low dose of aspirin; however, even this can cause minor haemorrhagic consequences in newborn infants.[25] Dipyridamole, however, is not known to be associated with fetal malformations.[27]

Our patient had a limited myocardial infarct in mid-pregnancy. She survived cardiac arrest associated with ventricular fibrillation, which fortunately occurred when she was already on a coronary care unit. Subsequent unstable symptoms were found to be associated with a tight stenosis of the left anterior descending coronary artery that was particularly suited to treatment by percutaneous transluminal coronary angioplasty. Exposure of the fetus to *x* rays was kept to a minimum. The application of this technique allowed the mother to have an angina free pregnancy, delivery, and puerperium, and she was delivered of a normal male infant. No decision has been reached regarding further pregnancies.

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Diagnosis of a right coronary artery-left ventricular fistula by cross sectional and Doppler echocardiography

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SUMMARY A case of right coronary to left ventricular fistula was diagnosed by cross sectional and Doppler echocardiography. The origin and site of entry into the left ventricle of the enlarged right coronary artery were shown by cross sectional echocardiography. Diastolic flow was detected in the left ventricle by both pulsed and continuous Doppler echocardiography. The fistula was confirmed by cardiac catheterisation and was successfully closed at operation.

Coronary artery fistula is a rare congenital anomaly in which the affected coronary artery empties into the left ventricle.[1-3] These fistulas can be identified by angiography but recent reports have shown the potential usefulness of non-invasive techniques.[4-6] We report a case in which a combination of cross sectional and pulsed and continuous Doppler echocardiography was used to image a coronary artery fistula and identify its site of drainage.

Case report

A 23 year old woman had a two year history of exertional dyspnoea, palpitation, and recurrent dizziness. Physical examination showed a normally developed young woman. Blood pressure was 140/90 mm Hg in both arms, and the pulse was 88 beats per minute and regular. There was no clinical evidence of cardiac enlargement. The first and second heart sounds were normal in quality and intensity. There was a grade 3/6 diastolic murmur over the central lower region of the sternum. The electrocardiogram showed left ventricular hypertrophy by voltage criteria. A chest *x* ray showed slight cardiomegaly with a circumscribed opaque round shadow at the right cardiophrenic angle (fig 1a).

At cardiac catheterisation the left ventricular end diastolic pressure was raised at 21 mm Hg. Coronary angiography showed a considerably dilated and tortuous right coronary artery (corresponding to the right paracardiac shadow) draining into the left ventricle (fig 1b). The left coronary artery was normal.

ECHOCARDIOGRAPHIC FINDINGS

We used an Aloka mechanical scanner Model SSD-118 for cross sectional echocardiography and a Toshiba phased array scanner SSH-40A for combined cross sectional and Doppler echocardiography. In the parasternal short axis view, the ostium of the right coronary artery (2 cm in diameter) was seen to originate from the aorta (fig 2a). The site of entry (1 cm in diameter) into the moderately enlarged left ventricle was shown just below the posterior mitral leaflet at the posteromedial region of the left ventricle in a parasternal short axis view (fig 2b). This corresponded with the angiographic findings. Both pulsed and continuous Doppler showed a diastolic flow pattern at the site of entry.

At operation, a dilated right coronary artery measuring 1·5 cm in diameter was found communicating with the inferior wall of the left ventricular cavity at the crux. The fistula was closed at its distal end by interrupted sutures. The patient was discharged in good condition on the seventh day after surgery and was free of symptoms at follow up six months later.

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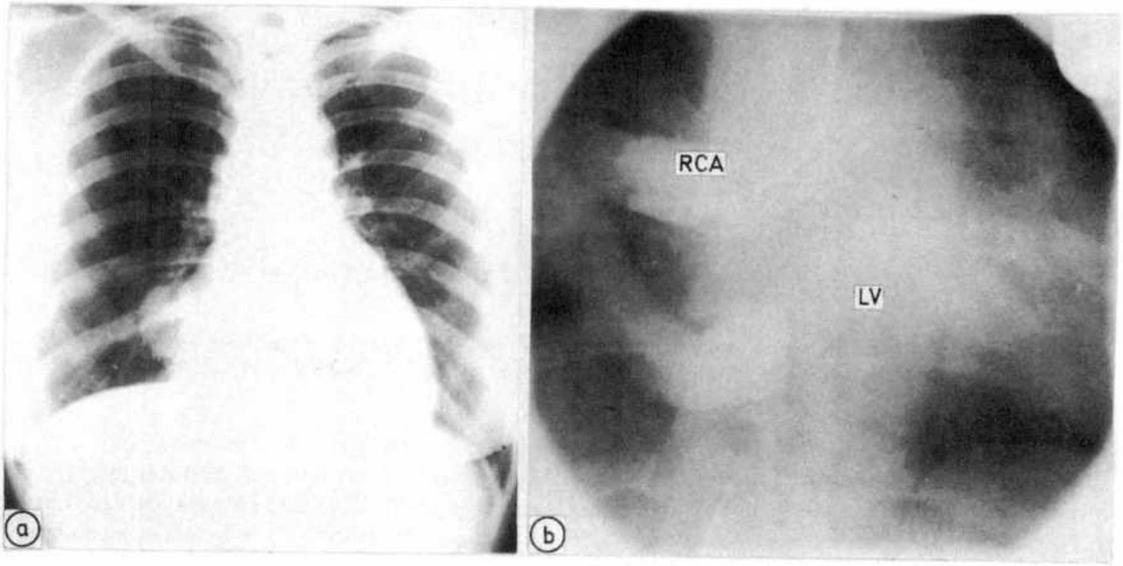

Fig 1 *(a) Chest x ray in posteroanterior projection showing mild cardiomegaly and normal pulmonary vasculature. There was an opaque shadow at the right cardiophrenic angle. (b) Right coronary angiogram showing a diffusely dilated, tortuous right coronary artery (RCA) that emptied into the left ventricle (LV).*

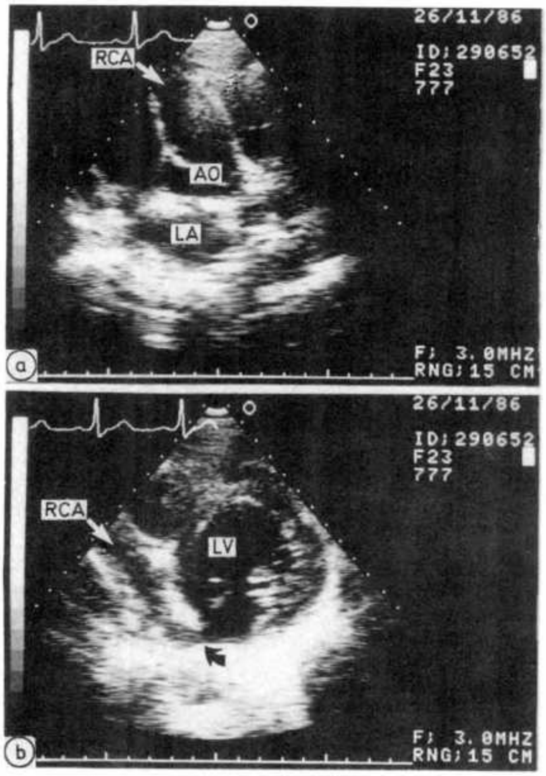

Fig 2 *Cross sectional echocardiogram showing (a) parasternal short axis view of the aorta (AO) at the level of aortic valve showing the markedly enlarged proximal right coronary artery (RCA) (arrow); (b) parasternal short axis view just below the mitral valve showing the distal right coronary artery (white arrow) draining into the left ventricle (LV). The site of entry into the left ventricle is indicated by the curved black arrow.*

Discussion

Cross sectional echocardiography has been used to image normal calibre coronary arteries and to demonstrate dilated coronary arteries associated with the mucocutaneous lymph node syndrome and with coronary artery fistulas.[7-9] Reeder *et al* used cross sectional echocardiography to visualise an aneurysmal coronary artery fistula and they concluded that contrast echocardiography was better than angiography for delineating the cardiac chamber into which the fistula emptied.[4] The identification of both distal and proximal portions of a coronary fistula by cross sectional echocardiography has also been reported.[4 10] Agatston *et al* used pulsed Doppler to confirm the site of the distal end of the fistula at the junction of the coronary sinus and right atrium.[11] Cross sectional visualisation of dilated proximal coronary arteries alone, however, does not indicate the presence of a coronary fistula.[5] It is often difficult to distinguish between fistulas and aneurysms of the coronary artery or anomalous origin of the coronary arteries. But Doppler echocardiography can identify continuous flow in the right heart chambers or diastolic flow in the left ventricle, and hence confirm the site of drainage of the fistula.[11 12]

Echocardiographic imaging of the dilated proximal portion and the distal end of the right coronary artery draining into the left ventricle just below the posterior mitral leaflet in this present case should therefore be sufficient for the diagnosis of a right coronary artery fistula to left ventricle. The portal of entry was detected by pulsed Doppler echocardiography and was confirmed by angiography and at operation.

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Balloon dilatation of a Waterston aortopulmonary anastomosis

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SUMMARY Percutaneous balloon dilatation of a Waterston anastomosis was performed in a child who had had four shunt operations. Initially, the procedure was apparently successful, but pulmonary oedema developed and he died 12 hours after the procedure.

Balloon dilatation of a Waterston anastomosis is technically possible and may prove to be an alternative to reoperation in certain patients. But further experience with the technique is necessary to determine the optimum size of the inflated balloon, and to avoid the risk of producing an excessive increase in pulmonary blood supply.

Percutaneous balloon dilatation is useful for the treatment of a wide variety of stenotic lesions associated with congenital heart disease. The technique may prove to be valuable for the dilatation of surgical aortopulmonary anastomoses; however, published data seem to be restricted to a single report of balloon angioplasty of a stenosed Blalock-Taussig shunt.[1] We report the case of a patient who had balloon angioplasty of a Waterston anastomosis after four shunt operations. The blood supply to the right lung was increased to such an extent that pulmonary oedema developed and he died 12 hours later.

Case report

A thirteen year old boy with pulmonary atresia and ventricular septal defect had had a Waterston shunt constructed in the neonatal period. Later he had a left Blalock-Taussig shunt when he was two and revision of this shunt when he was five. When he was nine he had an ascending aorta to left pulmonary artery Goretex shunt. The last operation was complicated by severe haemorrhage from multiple small collateral vessels. Four years after his last operation his cyanosis and exercise tolerance had again worsened. Reinvestigation showed that his principal pulmonary blood supply was to the right pulmonary artery from the 13 year old Waterston shunt. The central and main pulmonary arteries were occluded and there was only a scant collateral supply to the left lung. No true pulmonary arteries were identified on the left and the Blalock-Taussig and Goretex shunts were occluded. The diameter of the Waterston shunt was approximately 3 mm.

Under general anaesthetic and mechanical ventilation with 30% oxygen the right pulmonary artery was catheterised by a retrograde percutaneous approach from the right femoral artery with a 7 French Gensini catheter. A double length guide wire was positioned in the pulmonary artery supplying the right lower lobe and the Gensini catheter was replaced by an 8 mm Meditech balloon catheter. No waist was seen when the balloon was fully inflated. A 12 mm balloon catheter was substituted, and a clear waist was seen which abruptly disappeared on full balloon inflation. Repeat aortography showed that the size of the Waterston anastomosis had increased considerably. The pulmonary artery pressure abruptly rose to 42/30 mm Hg from 15/11 mm Hg, the aortic diastolic pressure fell to 46 mm Hg from 65 mm Hg, and the aortic oxygen saturation rose from 79% to 96%. He recovered rapidly from the general anaesthetic and seemed to be well; however, he had a collapsing pulse. Shortly afterwards clinical signs of frank pulmonary oedema developed and he was promptly reventilated. A chest radiograph showed pulmonary oedema and a pleural effusion on the right and considerable oligaemia on the left. Despite intensive supportive therapy he died 12 hours after dilatation.

Necropsy showed gross congestion and oedema of the right lung with a surrounding pleural effusion and confirmed the angiographic findings of pulmonary atresia with ventricular septal defect and occluded central and Blalock-Taussig shunts. There were dense mediastinal and pericardial adhesions and the heart was not enlarged. There was no extravas-

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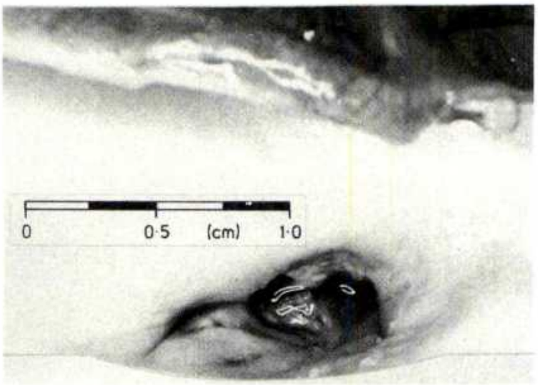

Figure *The orifice of the Waterston anastomosis viewed from the aorta. Dilatation was largely the result of disruption of the wall of the anastomosis, producing a V shaped tear in its inferior wall.*

cular evidence of trauma or haemorrhage surrounding the ascending aorta or the right pulmonary artery. The Waterston anastomosis had been enlarged to a maximum diameter of approximately 10 mm by a tear on its inferior aspect (figure), extending from the aorta into the proximal right lower lobe pulmonary artery. The tear included the intima and elastic and fibrous tissue of the aortic and pulmonary arterial walls, but did not extend into the dense scar tissue surrounding the anastomosis. Microscopy of the aortic wall at the anastomosis showed considerable fibroelastic intimal hyperplasia.

Discussion

Balloon angioplasty may be valuable for the relief of both branch pulmonary artery stenosis[2,3] and coarctation of the aorta.[4,5] The choice of the optimum size of the inflated balloon may be difficult because this depends not only on the severity of the stenosis but also on its site—that is, the elasticity of the lesion to be dilated. Balloon diameters $\geqslant 2{\cdot}5$ times that of the stenosis may be needed for the successful dilatation of narrowings of the branch pulmonary arteries or coarctation of the aorta[2-5] and balloon dilatation of the pulmonary valve may require balloon diameters that are up to 40% greater than the diameter of the valve annulus.[6] Postoperative narrowings of venous channels may be very compliant, and may require inflated balloon diameters of up to four or five times the diameter of the stenosis.[7] In a report of dilatation of a stenosed Blalock-Taussig shunt successful dilatation (three times the diameter of the stenosis) was eventually achieved with an inflated balloon with a diameter six times that of the stenosis,[1] suggesting that stenotic lesions involving the surrounding scar tissue may be the most elastic of all. Dense fibroelastic tissue was found within the aortic wall at the site of anastomosis in our patient.

It has been suggested that an increase of 2 mm in balloon size is warranted if no clear waist is seen on the initial balloon inflation when a stenosis of a branch pulmonary artery is being dilated.[3] This recommendation implies that the absence of a waist may predict unsuccessful dilatation. Because we thought that dilatation of the Waterston anastomosis in this case would be difficult to achieve, we chose to increase the balloon size by 4 mm and this resulted in overdilatation, with a final anastomosis diameter of about 80% of the inflated balloon diameter. In retrospect, it seems possible that despite the absence of a balloon waist our initial dilatation might have been successful. This experience prompts us to recommend detailed haemodynamic reappraisal and measurement of systemic arterial oxygen saturation after each balloon inflation irrespective of the radiographic appearances during balloon inflation.

The absence of postmortem evidence of an increase in heart size in our patient is also of note. Multiple thoracotomies may be followed by extensive mediastinal fibrosis, and the dense pericardial adhesions seen in this case may well have compromised the ability of the heart to dilate and increase its stroke volume to cope with a sudden increase in pulmonary blood flow.

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An unusual presentation of right coronary artery fistula

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SUMMARY A four year old girl with infective endocarditis had unexplained facial swelling. Cross sectional echocardiography showed that a large right coronary artery fistula to the right atrium was obstructing the distal superior vena cava. The diagnosis was confirmed by cardiac catheterisation and at operation. The child was symptom free one year after operation.

Coronary artery fistula is a rare congenital heart lesion[1 2] which is diagnosed in most instances in young patients who present with atypical murmur.[3] The definitive diagnosis relies on cardiac catheterisation although several cases diagnosed by cross sectional echocardiography have been reported recently.[4-6]

The haemodynamic complications of a coronary artery fistula are usually related to an important left to right shunt, ischaemic heart disease (caused by coronary artery steal), or accelerated atherosclerosis (in the older patient). Infective endocarditis, thrombosis, and rupture of the fistula may occur. In rare instances the fistula may obstruct one of the cardiac vessels or cavities. We report a rare case of a right coronary artery fistula that caused obstruction of the superior vena cava.

Case report

A four year old girl with no previous cardiac symptoms was referred with fever, lethargy, arthralgia, and episodes of facial swelling that had started six months before admission to hospital. On examination she was well developed, blood pressure was 90/50 mm Hg, the pulse was normal with a rate of 100 beats per minute, and her face was swollen. There was finger clubbing. A diffuse cardiac apex was felt at the sixth intercostal space in the anterior axillary line. Heart sounds were normal. A 2/6 continuous murmur was heard over the right sternal border and a 3/6 early diastolic murmur was detected over the aortic valve area. The liver and spleen were enlarged (6 and 10 cm respectively below costal margin). The biochemical and haematological laboratory results were within normal limits; the erythrocyte sedimentation rate was 35 mm in the first hour. The electrocardiogram and chest *x* ray were normal. The clinical diagnosis of infective endocarditis with aortic valve regurgitation was supported by finding viridans streptococci in multiple blood cultures.

Cross sectional echocardiography (Diasonic CV 400, 3 5 MHz transducer) showed a 5 mm vegetation on the right coronary cusp and Doppler echocardiography showed mild aortic regurgitation. The unexpected finding of a very dilated proximal right coronary artery (14 mm in diameter) raised the suspicion of a coronary artery pathology. The origin of the left coronary artery from the aorta was well visualised. From the subcostal short and long axis views a large right sinus of Valsalva was seen and a dilated proximal right coronary artery could be followed. It started from a normally located ostium and ran conventionally in the right anterior atrioventricular groove. At Doppler examination turbulent flow was found above the aortic valve in the right sinus of Valsalva. From the second third of the right coronary artery, just distal to the origin of the acute marginal branch, a fistula was seen running posteriorly toward the superoposterior portion of the interatrial septum (sinus venosus area) and ending over the right aspect of the interatrial septum as a distal spherical aneurysm (fig 1).

Doppler examination around the aneurysm showed high velocity turbulent flow but the exact location of the communication with the right atrium could not be visualised. The entrance of the superior vena cava into the right atrium was very narrow (2

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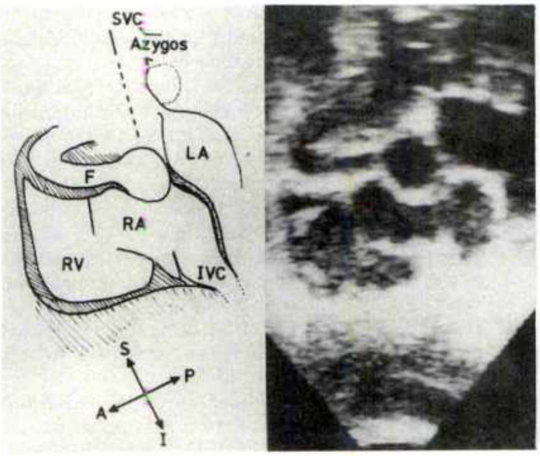

Fig 1 *Subcostal short axis echocardiogram and diagram showing the pathway of the right coronary fistula and the aneurysm in the right atrium. SVC, superior vena cava; F, fistula; RV, right ventricle; RA, right atrium; LA, left atrium; IVC, inferior vena cava.*

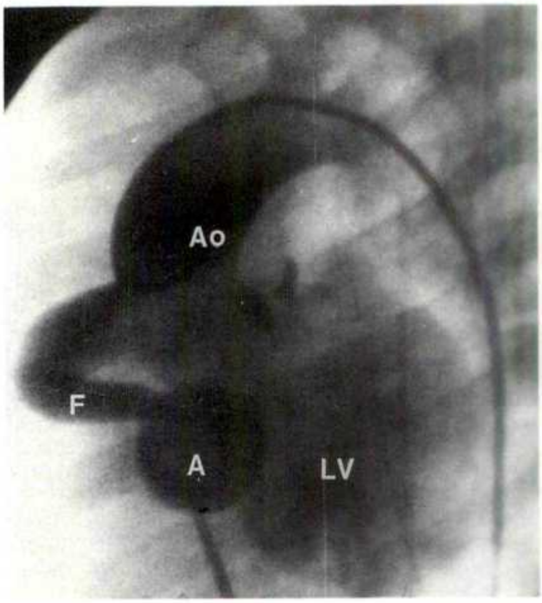

Fig 2 *Supravalvar aortogram in left anterior oblique projection showing the large right coronary artery and the fistula (F) ending in an aneurysm (A). There is slight opacification of the left ventricle (LV) owing to aortic regurgitation. Ao, ascending aorta.*

mm) because it was compressed by the dilated fistula. There was no sign of right ventricular volume or pressure overload.

Cardiac catheterisation was undertaken to confirm the anatomical diagnosis. Special attention was paid to the distribution of the branches of the right coronary artery (fig 2). No left to right shunt was detected by measurements of oxygen saturation; none the less, contrast injection in the proximal right coronary artery showed mild opacification of the right atrium, ventricle, and pulmonary artery. The pathway of the fistula was confirmed by selective injection into the right coronary artery. Small marginal branches were visualised as they branched from the dilated right coronary artery. The superior vena cava could not be entered from the right atrium. A digital subtraction angiography was then performed by injecting 4 ml of contrast material in the right external jugular vein. A near total obstruction of the distal superior vena cava was shown; a very small amount of contrast material directly entered the right atrium from the superior vena cava while most of the contrast material drained into a dilated azygos vein towards anastomoses with the inferior vena cava.

Operation confirmed the anatomical diagnosis and the patient had ligation of the fistula and patch augmentation of the distal superior vena cava. She was symptom free a year after operation.

Discussion

A congenital coronary artery fistula is a rare anomaly. It was found in 1 out of 50,000 children with congenital heart disease.[1,2] Several groups have shown that cross sectional echocardiography shows the anatomy of the fistula, its pathway, and its correlation to adjacent structures.[4-6] Moreover, the haemodynamic effects of the fistula can be studied by Doppler echocardiography, which can detect a fistula-to-cavity shunt and estimate the shunt ratio.[7,8] In this child the detailed pathway of the fistula, its connection to adjacent cardiac structures, and a restrictive left to right shunt were shown. In fact, the main reason for undertaking cardiac catheterisation was to ascertain the branching of the right coronary artery—a feature that was not shown by cross sectional echocardiography. Infective endocarditis is not often associated with coronary artery fistulas, but there are several published reports of such cases.[2,9-11] The dilatation of the right sinus of Valsava with the turbulent flow across the aortic valve that we saw in our patient might have enabled bacterial colonisation over the right coronary cusp. The compression of the superior vena cava by the aneurysm in the right atrium in our patient is unusual and to our knowledge has not been described before.

This case shows that a coronary artery fistula may present obstruction of the superior vena cava. Although the fistula and its pathway were easily diagnosed by cross sectional echocardiography, cardiac catheterisation was needed to show the course and anatomy of the affected coronary artery. The defect was corrected at operation with excellent results.

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Proceedings of the British Cardiac Society

THE 67TH ANNUAL GENERAL MEETING of the British Cardiac Society was held at the Belfast City Hospital on Wednesday and Thursday, 23 and 24 March 1988. The President, E Sowton, took the Chair during private business. R H Swanton succeeded D J Coltart as Secretary, P J Oldershaw was elected Assistant Secretary, and R W F Campbell was elected to Council on the retirement of D J Rowlands.

Deaths during the year: C W C Bain, C E Drew, R E B Hudson, A Hunter, O Kerr, C Symons, Helen Taussig.

New Ordinary Members 1988: N J Archer (Oxford); E J Baker (London); S G Ball (Leeds); J Beattie (Birmingham); S Campbell (Oxford); K S Channer (Bristol); R Collins (Oxford); J E Creamer (Manchester); A D Cunningham (London); A Davies (Middlesbrough); D W Davies (London); Heather M Dunn (Londonderry); A E Evans (Belfast); I N Findlay (Glasgow); E Jane Flint (W Midlands); M George (N Devon); A H Gershlick (London); B A Gould (Bristol); W J Grabau (Norfolk); L Guvendik (London); A M Heagerty (Leicester); R S Hornung (Glasgow); Patricia J Lowry (Birmingham); J M McLenachan (Glasgow); Jennie M Metcalfe (London); P Nihoyannopoulos (London); J E F Pohl (Leicester); Julia M Polak (London); P M Schofield (Liverpool); M Signy (London); W C S Smith (Dundee); L B Tan (Oxford); Ann C Tweddel (Glasgow); G I Verney (Cambridge); S C Webb (London); D A Wood (Southampton).

New Honorary Members: W Nelligan (USA); A Selzer (USA).

New Corresponding Members: S Furman (USA); M Kyriakidis (Greece).

New Overseas Member: Carole A Warnes (USA).

During the meeting the scientific sessions were held under the chairmanship of D Boyle and the following are abstracts of the papers that were presented.

Preliminary use of a dynamic rotating tip catheter for recanalisation of occluded vessels

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Dynamic angioplasty (Kensey catheter) is a new treatment for vascular disease. The system consists of a French 8 catheter with a motor driven rotating cam at its tip that is capable of speeds of 90 000 rpm. The catheter has an inner lumen for the drive shaft and a fluid channel. The fluid is pumped through the catheter as a fine jet that is directed radically by the spinning of the cam. The rotating tip and the fluid jet abrade atheroma and calcified plaque but do not affect elastic tissue. We report the first use of this in the United Kingdom in five men with occlusive peripheral disease (four femoral/popliteal occlusions, one iliac occlusion), in whom conventional angioplasty had been unsuccessful. All five patients have showed significant clinical improvement after dynamic angioplasty. Two patients had complete occlusions recanalised with dynamic angioplasty (11 cm and 16 cm occlusions). One patient had recanalisation with a combination of dynamic and conventional angioplasty; the other two patients had partial recanalisation. In one patient a distal embolus developed eight h after the procedure; this was successfully treated with local streptokinase. Doppler pressures were measured before and after the procedure in four patients and showed improvement. In three of these patients clinical and Doppler improvements were confirmed by measurement of limb blood flow by radionuclide angiography.

Immediate and long term follow up after percutaneous transluminal coronary angioplasty: comparison of stable and unstable angina pectoris

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The clinical outcome of the first 896 consecutive patients (1000 lesions) who had percutaneous transluminal coronary balloon angioplasty (PTCA) between September 1980 and November 1985 was assessed. PTCA was performed in 530 patients who presented with stable angina pectoris (group 1) and in 366 with unstable angina pectoris (group 2). Follow up data were assessed at three different times: within 24 hours of the procedure, within six months, and at the last available follow up (mean 2·1 years) after the procedure. Twenty six per cent of the procedures were done before the introduction of the steerable guiding systems in February 1983. There was no difference in the primary success rate (group 1 83%, group 2 87%) nor in the annual mortality rate, which was approximately 2% per year for both groups. In the group with unstable angina pectoris (group 2) the incidence of acute myocardial infarction within the first 24 hours was higher (9% versus 4%) and this difference persisted at the six month and long term follow up examinations. There was also an increased rate of coronary bypass surgery in group 2 at both six month and long term follow up (17% *vs* 13%, and 21% *vs* 15% respectively). There was no difference in frequency of repeat PTCA. At six month follow up 71% of group 1 and 72% of group 2 were event free in terms of death, myocardial infarction, coronary bypass surgery, and repeat PTCA. At long term follow up the percentages were 69% and 61% respectively.

What factors predict recurrent restenosis after coronary balloon angioplasty?

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Massachusetts, USA

Restenosis after percutaneous transluminal coronary angioplasty (PTCA) has been much investigated, but scant attention has been paid to those patients who have recurrent ($\geqslant 2$) restenoses of their initial lesions. To determine the frequency of recurrent restenosis after PTCA and the factors that may predict this occurrence we examined the records of 1011 patients undergoing PTCA in our centre from 1 March 1980 to 1 June 1987. Of these patients, 262 (26%) had a single restenosis of one or more of their initial lesions and 38 (3·8%) had recurrent restenosis. We selected a random sample of 125 patients (group A) from among those patients with a single restenosis and compared their characteristics with those of the 38 patients with recurrent restenosis after PTCA (group B). There was no significant difference between the two groups for age and sex distribution, angina state, clinical presentation at the time of angioplasty, frequency of coronary risk factors, and coronary angiographic features. Univariate analysis of procedural factors showed that important predictors of recurrent restenosis were a greater number of inflations (6·3 (3·9) (mean (SD)) in group B patients and 4·9 (2·7) in group A; $p < 0{\cdot}01$) and a shorter balloon inflation time (50 seconds (mean) in group B and 64 seconds (mean) in group A; $p < 0{\cdot}06$). Neither the maximum balloon inflation pressure nor the balloon size predicted recurrent restenosis.

These data indicate that the recurrent restenosis rate after angioplasty is low and may be reduced by careful attention to procedural details, in particular, by use of fewer but longer inflations.

Assessment of regional wall motion abnormalities during coronary angioplasty by an algorithm of coronary artery shortening: correlation with changes in regional blood flow and myocardial metabolism

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M F Shiu
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Balloon occlusion during coronary angioplasty causes ischaemia of the myocardium distal to the balloon and induces abnormalities of left ventricular wall motion. Assessment of this regional contractile dysfunction during balloon occlusion is difficult. We have previously used shortening of the coronary artery branch junction as a measure of myocardial contraction and have now studied changes during angioplasty using a computer assisted algorithm for sequential frame tracking of branching points. We studied 12 men undergoing elective angioplasty to the left anterior descending artery. In addition to measurements of great cardiac vein flow (GCVF), myocardial oxygen consumption (MVo_2), and lactate production (LER) the distal arterial lumen was imaged during the last 10 s of a 60 s balloon inflation by injecting dilute contrast through the distal balloon lumen. The relative maximal percentage shortening of septal branching points through a cardiac cycle during the second balloon inflation was compared with control films. Arteriograms were digitised on an Olivetti M24 PC and a semiautomatic tracking program was used to enter branching points on sequential frames. The mean percentage end diastolic to end systolic branch shortening during control films was 17 (9)%. This was significantly lower during balloon occlusion 5 (10)% ($p < 0{\cdot}0001$). There was also a significant fall in GCVF

(106 (87 to 76 (58) ml/min; $p < 0{\cdot}02$), MVo_2 (11 9 (4·2) to 9 9 (4·0), $p < 0{\cdot}05$), and LER (70 (52) to 6 (15); $p < 0{\cdot}02$). There was a significant correlation between the reduction in branch shortening and the changes in GCVF, MVo_2, and LER ($r = 0{\cdot}6$, $p < 0{\cdot}02$).

Shortening of the coronary artery branch junction is a simple and easily repeatable measurement for assessing regional wall motion during angioplasty. There is a significant correlation between these observed wall motion abnormalities and the reduction in regional flow and changes in regional metabolism induced by balloon occlusion.

Angioplasty of total coronary occlusions: improved success rates with the use of a wire splinting technique

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For chronic total coronary artery occlusion recanalisation by percutaneous transluminal coronary angioplasty (PTCA) is increasingly considered. The conventional technique is to explore and cross the occluded segment with the soft steerable wire and to attempt balloon passage across the lesion only if it can be crossed with a wire. The success rate of PTCA of total coronary occlusions is significantly lower than that of non-occluded vessels and the failures are the result of the inability of the soft flexible tip of steerable wire to cross the occlusion. We have developed a new technique of splinting the floppy tip of the steerable wire with the balloon catheter which permits crossing and successful dilatation of a higher proportion of chronic total occlusions. PTCA was performed on 46 totally occluded coronary arteries in a series of 354 elective PTCA procedures. Procedures for acute myocardial infarction are excluded from this series. Successful dilatation leading to revascularisation was achieved in 68% (31/46). There were no major complications. Duration of occlusion was less than two months in 20 patients (group 1), 2–6 months in 11 (group 2), and more than six months in 15 (group 3). The success rate decreased with duration of occlusion: 80% in group 1, 73% in group 2, and 46% in group 3. Until June 1986 only the conventional technique was used (period A) and after June 1986 the "wire splinting technique" was applied if the conventional technique failed. Twenty total occlusions were attempted in period A and 26 in period B. Though the success rates for occlusions of less than two months' duration in the two periods were not significantly different, the success rates for longer standing occlusions (more than two months) were 3/10 in period A *vs* 12/16 in period B ($p < 0{\cdot}05$).

The wire splinting technique is safe and led to a higher rate of successful revascularisation of longstanding total coronary occlusions than the currently published series. These results also have implications for the design of balloon catheters.

Laser coronary angioplasty under direct vision

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We have developed a system of angioscopy that uses a 2·5 mm flexible angioscope with a working channel for laser angioplasty. The angioscope has an integral coherent optical bundle for visualisation and two working channels. A 400 µm glass fibre is inserted into one channel and is used for illumination. The other channel is for saline flushing. The 400 µm fibre can be attached to an Nd-YAG laser for illumination by the helium-neon aiming beam. The fibre can be manoeuvred into position by extending it from the end of the angioscope once the target has been visualised. It therefore has a dual role—illumination and transmission of laser energy. A video will be shown of the angioscope being used to create a laser channel through a stenosis in the right coronary artery of a postmortem heart.

Coronary artery surgery in the elderly is effective in the relief of angina

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Financial constraints may prevent older patients from being considered for coronary artery bypass grafting (CABG). CABG was performed on 315 elderly patients (244 men, age 65–79, mean 68 years) between 1981 and 1986. All patients had limiting angina; 38% had rest pain and 80% had triple vessel disease. There was no impairment of left ventricular function in 46%, mild impairment in 20%, moderate impairment in 23%, and severe impairment in 10% of patients. Grafts (saphenous vein or internal mammary artery) were inserted into three vessels (52%), four vessels (42%), five vessels (6%), and six vessels

(0·5%). Operative mortality (< 24 hours) was 1·6% and a further 3·2% of patients died later during the same admission. Seventy per cent of patients who died had moderate or severe left ventricular impairment before operation. Surgical complications included myocardial infarction (8%), transient cerebrovascular ischaemia (5%), cerebrovascular accident (1%), transient renal dysfunction (4%), chest infection (10%), and wound infection (4%). Median stay on the intensive care unit was one day and median total hospital stay was 12 days. Two hundred and ninety nine patients survived to leave hospital and follow up data are available for 217 (72%) of them. Ninety six per cent were subjectively improved by operation; 88% were free of angina off all antianginal drugs a median of 72 weeks (range 8–307) after operation and 8% were not limited by angina on medical treatment a median of 85 weeks (range 9–302) after operation.

We conclude that CABG is an effective treatment in the elderly. Its risks, complications, and morbidity compared favourably with those of hip replacement.

Minor changes in QRS configuration during unstable angina: evidence for recurrent myocardial "micro-infarctions"?

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Myocardial "micro-infarctions" can follow peripheral microthromboembolism during unstable angina; their frequency is, however, unknown. Similar size lesions in animals cause minor distortion of QRS configuration on high-fidelity recordings. To determine whether such changes occur in man we compared QRS configurations in high-fidelity vectorcardiograms recorded over three successive days from 24 patients with unstable angina of recent onset (without evidence of infarction on 12 lead electrocardiograms) and 20 patients with stable angina on effort. High resolution QRS complexes were derived by signal averaging of unfiltered Frank lead vectorcardiograms in duplicate over 100 beats by use of a trolley mounted microcomputer system with 1 KHz sampling frequency and 12 bit resolution. Minor distortions of QRS configuration were quantitated from "counts" of inflections of the derived instantaneous spatial velocity of the QRS vector loop (that is $\sqrt{\ ((dx/dt)^2 + (dY/dt)^2 + (dZ/dt)^2)}$). Inflection "counts" ranged from 5 to 27 in individual patients and were highly reproducible in duplicate recordings ($r = 0{\cdot}99$). The initial distribution of inflection "counts" was similar in the groups with stable and unstable angina (16·7 (3·8) *vs* 15·6 (4·8) "counts"). Over the three successive days, however, 8/24 (33%) of patients with unstable angina showed either loss of spatial velocity inflections or appearance of new inflections outside the ranges seen in stable angina (mean Δ "counts" 2·9 (2·9) *vs* 0·7 (0·9) $p < 0{\cdot}01$).

Results suggest that minor changes in QRS configuration consistent with the development of minor areas of myocardial infarction or "micro-infarction" may be detectable in about one third of cases of unstable angina.

Distribution of receptors for calcitonin gene related peptide (CGRP)—a potent vasodilator—in human and guinea pig heart

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The factors which control coronary artery tone are incompletely understood but is likely that several recently described peptides have a role. One such peptide, CGRP, is a potent vasodilator that has been shown by immunohistochemistry to be abundant in nerves around coronary arteries and is also found in the circulation. CGRP acts on specific receptors located on smooth muscle. Using autoradiographic techniques we have demonstrated the receptor for CGRP in both guinea pig heart and human heart removed at transplantation and have compared the distribution of these receptors in various cardiac tissues. Human cardiac tissue was removed from three patients undergoing transplantation for end stage ischaemic disease. The receptor density in various areas of the heart was compared by counting the binding sites (BS) in 12 separate highly magnified areas from each region studied. In the guinea pig heart the concentration of receptors (> 250 BS/1000 μm^2) in the major coronary arteries and veins was high. Lower concentrations (50–150 BS/1000 μm^2) were found on arterioles, great vessels, and endocardium and no receptors were detected on myocardium or stroma. Similar values were found in human tissue. In a single atheromatous artery the concentration of CGRP receptors resembled that of a normal artery from the same patient but in a thrombosed vessel the concentration was considerably reduced.

This technique permits localised changes in receptor function to be studied in situ and it showed that specific receptors for CGRP occurred in large numbers in the coronary arteries. This evidence may support a role for CGRP in regulation of coronary tone although further studies are necessary.

Sustained activation of cardiac sympathetic tone in unstable and post-infarction angina

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The cardiac sympathetic nervous system has a profound effect on the susceptibility of the ischaemic myocardium to serious ventricular arrhythmias, and alterations in cardiac autonomic tone have been implicated in sudden ischaemic cardiac death. We used 1-[^{3}H] noradrenaline (NA) kinetics to evaluate sympathetic activity in 20 patients with ischaemic heart disease: 10 with recent ($\leqslant$12 weeks) unstable or post-infarction angina (group U) and 10 with chronic stable angina (group S). Plasma NA (333 (64) pg/ml in group U, 210 (30) pg/ml in group S) and whole body NA spillover (375 (56) ng/min in group U, 286 (23) ng/min in group S) tended to be higher in group U but not significantly so. In contrast, coronary sinus NA (515 (117) pg/ml in group U, 171 (24) pg/ml in group S, $p < 0{\cdot}001$) was increased in the patients with unstable angina. Cardiac NA spillover, which reflects cardiac sympathetic tone, was also greatly increased in the patients with unstable angina (24 5 (6·9) ng/min in group U, 6·1 (1·3) ng/min in group S, $p < 0{\cdot}001$). Coronary sinus plasma flow and cardiac NA clearance were similar in both groups.

This study shows that patients with unstable ischaemic symptoms, who are known to be at increased risk of sudden cardiac death, have evidence of a sustained and specific increase in cardiac efferent sympathetic tone. This supports the theory that sympathetic overactivity is an important factor in causing serious ventricular arrhythmias in ischaemic heart disease.

Do the investigation for and treatment of oesophageal abnormalities improve the outcome of patients with angina pectoris, normal coronary angiograms, and normal left ventricular function?

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A postal questionnaire was used to assess the symptoms, use of medical facilities, and employment state of patients with angina pectoris and normal coronary angiograms after cardiac catheterisation. In a retrospective study of 187 patients, 66 had left ventricular dysfunction (LVD) shown by abnormal regional wall motion and 121 had normal left ventricular function (NLV). At follow up 12–46 months after catheterisation 89% of patients with LVD and 82% of those with NLV continued to experience chest pain. There was no significant change in the rate of admission to hospital because of chest pain or in the proportion of patients who were working after compared with before catheterisation in either group. In a prospective study of 63 patients detailed investigation of oesophageal function was performed. Twenty two patients had LVD. Most of the 41 patients with NLC had oesophageal abnormalities (gastro-oesophageal reflux or oesophageal dysmotility, or both), which were treated appropriately. At follow up 6–24 months after catheterisation significantly fewer patients with NLV than patients with LVD continued to experience chest pain (67% *v* 90%, respectively; $p < 0{\cdot}05$). The rate of admission to hospital fell significantly after catheterisation in patients with NLV (mean 0·068 (SD 0·076) to 0·008 (0 022) admissions/month; $p < 0{\cdot}01$) but not in those with LVD (0·065 (0·077) to 0·047 (0·047) admissions/month). The proportion of patients working after catheterisation increased significantly in those with NLV (from 49% to 74%; $p < 0{\cdot}05$) but not in those with LVD (from 52% to 48%).

The findings suggest that investigation for and treatment of oesophageal abnormalities improves the symptoms and employment state of patients with angina pectoris, normal coronary arteries, and NLV and reduces their use of medical facilities.

Free radical generation during pacing induced myocardial ischaemia

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Free radical generation occurs in experimental models of myocardial ischaemia and reperfusion and may cause cellular damage by peroxidation of membrane phospholipids. To determine whether free radical generation occurs during transient myocardial ischaemia in man we measured aortic and coronary sinus concentrations of malondialdehyde (MOA), an end product of lipid peroxidation. Twenty two patients (16 male) undergoing diagnostic coronary arteriography were studied during incremental atrial (or ventricular) pacing until the development of severe chest pain, a 2 mm ST segment depression, or a paced rate of 180 beats/min. Group 1 ($n = 11$) produced lactate during pacing, whereas group 2 ($n = 11$) continued to extract lactate throughout the study. All patients in group 1 and four in group 2 had coronary artery disease. Coronary sinus MOA values (median (interquartile range)) in group 1 were significantly increased from baseline at peak pacing rate (0·116 (0·112 to 0·126) *v* 0·120 (0 117 to 0 134); $p = 0·035$); at 30 seconds after pacing (0·129 (0·115 to 0·131); $p = 0·032$); and at 5 minutes (0·134 (0·126 to 0·143); $p = 0·036$). No differences with pacing were observed in the coronary sinus MOA values in group 2 or in the aortic MOA values in either group.

These results suggest that intramyocardial free radical generation occurs during transient myocardial ischaemia in man.

Relative efficacy of various physical manoeuvres in termination of re-entrant supraventricular tachycardias

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Physical manoeuvres are often attempted to terminate supraventricular tachycardia (SVT). We studied the relative efficacy of four different manoeuvres in terminating induced SVT and related the findings to the changes in heart rate caused by the manoeuvres in sinus rhythm. Twenty five patients (16 men) of mean age 36 years (range 16–69) with inducible SVT were studied. SVT was initiated by programmed stimulation. The response to right and left carotid sinus massage for 5 s each, face immersion in water at 5–19°C, and the Valsalva manoeuvre (VM) for 15 s (blowing at pressure of 35 mm Hg) were measured with continuous electrocardiographic recording at 50 mm/s during both sinus rhythm and SVT. If SVT was terminated it was reinitiated and the manoeuvre repeated two times to evaluate consistency. VM was most successful in terminating SVT (13 out of 25), especially when the patients were supine (13 out of 25 compared with two out of 25 standing; $p < 0·001$). Right carotid massage was effective in four patients, left carotid sinus massage in one, and face immersion in three. VM was more effective in younger patients (median = 29 years (16–44) *v* 44 years (17–69) conversions and non-conversions, respectively, $p < 0·02$) and in atrioventricular tachycardia (12 out of 18) compared with atrioventricular nodal tachycardia (one out of seven; $p < 0·03$). During sinus rhythm the RR interval increment expressed as a ratio was greatest with the VM (1·74 (0·38)) and progressively less with face immersion (1·26 (0·27); $p < 0·001$ when compared with VM), right carotid massage (1·25 (0·32), and left carotid massage (1·1 (0·17)). The VM ratio was higher in those in whom the manoeuvre successfully terminated SVT (1·88 (0·39) *v* 1 58 (0·32); $p < 0·06$).

In conclusion, VM was the most successful physical manoeuvre in terminating induced re-entrant SVT. It was more commonly effective in younger patients and in those with atrioventricular re-entrant tachycardia. The heart rate response to the VM during sinus rhythm related weakly to its effectiveness in terminating SVT.

Identification of major arrhythmias by retrospective patient activated monitor after negative conventional Holter recordings

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The problem of identifying (or excluding) a cardiac arrhythmia as the cause of transient symptoms has not been solved by 24 hour Holter electrocardiographic tape recordings (HTR) except in those patients in whom the episodes are frequent enough to occur during the recording. Moreover, asymptomatic arrhythmias detected on HTR may be treated, often without relieving the symptoms and sometimes leading to complications. A new alternative, the retrospective patient activated monitor (RPAM), can be used continuously for two weeks or longer if the battery is changed. The electrocardiogram (ECG) is stored in digital form by continuously overwriting a circular solid state memory. This stops after the device is activated by the patient so that 150 seconds of retrospective and 10 seconds of prospective ECG is saved and can be replayed on a standard ECG machine. We have used RPAM on 27 patients in whom HTR had failed to capture a symptomatic episode. In 10 patients no attack occurred during 2–8 weeks of investigation. In six patients the typical symptoms were associated with normal sinus rhythm, mild sinus tachycardia (up to 120 beats/min), or appropriate VDD (atrial synchronous) pacing. In a further five patients minor arrhythmias (atrial or ventricular extrasystoles) were recorded that required no treatment apart from reassurance. Major arrhythmias were identified in six patients: sinus arrest or severe bradycardia, or both, in two; paroxysmal supraventricular tachycardia in three; and ventricular tachycardia in one. Repeat studies were performed in five patients: in two because the lead or electrode, or both, had become disconnected; in one because of inadvertent activation; and in three because the attacks were considered to be not quite typical. In all five patients the second result was the same. Diagnostic information was thus gained in 17 out of 27 patients (63%).

We conclude that the RPAM is a valuable tool and may displace HTR as the primary investigation for patients with suspected paroxysmal arrhythmia.

Rapid exhaustion of atrial natriuretic peptide during sustained tachycardia

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To assess the ability of the atria to maintain raised plasma concentrations of atrial natriuretic peptide (ANP), the temporal changes in plasma ANP concentrations were studied during four hours of sustained rapid cardiac pacing in seven dogs anaesthetised with chloralose. Heart rate increased from (mean (SEM)) 124 (26) to 278 (28) beats/min during the four hours of rapid cardiac pacing. At 30 minutes pulmonary wedge pressure increased from 3·6 (1·8) to 17·4 (7·1) mm Hg ($p < 0\cdot01$) and mean right atrial pressure rose from −1·7 (1·9) to 2·0 (2·8) mm Hg ($p < 0\cdot01$). Both pressures remained constant at these raised values for the entire 240 minutes of rapid pacing. Arterial ANP concentrations increased from 87 (11) pmol/l to a maximum of 1263 (592) pmol/l at 30 minutes ($p < 0\cdot01$), falling to 411 (42) pmol/l after 60 minutes and 146 (70) pmol/l after 240 minutes of rapid continuous pacing ($p < 0\cdot01$ compared with value at 30 minutes). Coronary sinus ANP concentrations showed a similar pattern, rising from 241 (79) to a maximum of 1837 (203) pmol/l after 30 minutes ($p < 0\cdot01$). These peak values likewise were not sustained, falling to 962 (198) pmol/l after 60 minutes and 297 (41) pmol/l after 240 minutes of rapid pacing ($p < 0\cdot01$ compared with value at 30 minutes).

We conclude that atria are unable to maintain the peak concentrations of ANP reached after 30 minutes of rapid pacing despite persistently raised atrial pressures. Sudden sustained increases of atrial pressure, as occur during acute myocardial infarction, may rapidly exhaust stores of ANP with the loss of its natriuretic, vasodilator, and renin inhibiting actions.

Successful treatment of supraventricular tachycardia with an antitachycardia pacemaker: European results with Orthocor II

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As part of a prospective study conducted at 10 European evaluation centres, 24 patients (6 men, 18 women; age 35–78 years) with resistant supraventricular tachycardia (SVT) were treated with Orthocor II, an implantable antitachycardia device with additional "on board" Holter and non-invasive electrophysiological facilities. Devices were implanted between June 1984 and January 1987 after full electrophysiological study, with at least 20 tachycardia inductions and terminations by electrostimulation. Tachycardia was also repeatedly initiated and terminated automatically by the pacemaker before discharge. Data for these procedures and for up to 24 months' follow up were collected. Mechanism of SVT was atrioventricular nodal reentry in eight patients, Wolff-Parkinson-White syndrome in four, accessory bypass tract in four, and not further specified in eight. Rate of SVT was 130–240 (mean 181) beats/min with an estimated 1–300 (mean 5·3) occurrences a week. Endocardial lead position was atrial in 21 patients and ventricular in three. Tachycardia recognition criteria were 4–15 (mean 6·3) beats counted, at 120–180 (mean 145) beats/min. The automatic antitachycardia mechanism selected was burst rate scanning (20 patients) and automatic burst (one), with 1–10 (mean 5·9) extrastimuli used. Automatic overdrive was used in the remaining three patients. After implantation, the duration of tachycardia was reduced from 5–500 (mean 126) minutes to 6–130 (mean 31) seconds. The patient's condition was judged to have improved in 18 out of 24 (not specified in the six others), with drug treatment being reduced or eliminated in 17 (not specified in five patients). Discriminating sinus tachycardia from SVT was a problem in one patient with a low rate of tachycardia. No episodes of acceleration of tachycardia were reported; there were no explantations and no pacemaker related deaths.

This study confirms that implantable antitachycardia pacemakers provide a highly effective means of treating resistant SVT and that Orthocor II is itself a safe and reliable device.

Does the site of origin of ventricular tachycardia predict the presence of late potentials?

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In 20–40% of patients with inducible ventricular tachycardia (VT) no late potentials are detected in sinus rhythm. This may be owing to the early activation of the VT origin in sinus rhythm and the late potentials being hidden. This study examines whether the site of origin of the tachycardia, as determined by its axis and morphology, is associated with the detection of late potentials. Thirty two patients (mean age 54 years) with VT were studied. Patients with bundle branch block (BBB) in sinus rhythm were excluded. Late potentials were recorded in sinus rhythm with the standard Simpson technique using orthogonal leads (X, Y, and Z). A test was positive if the filtered QRS was greater than 120 ms or the root mean square of the last 40 ms was less than 25 μV, or both. Late potentials were detected in 10 out of 16 patients with ischaemic heart disease, seven out of 14 with morphologically normal hearts, and one of the two patients with congestive cardiomyopathy. Late potentials were present in eight out of 17 patients with left BBB pattern VT and 10 out of 15 with right BBB pattern VT. Multiple morphologies were present in eight patients, four of whom had late potentials. None of these differences approached significance, but 11 out of 13 patients with a superior axis and six out of 17 with an inferior axis during VT had late potentials ($p < 0{\cdot}01$). Both axes were present in two patients, one of whom had late potentials. This pattern persisted when the patients with and without ischaemic heart disease were analysed separately, though it only remained significant for patients with ischaemic heart disease ($p < 0{\cdot}05$).

To conclude, this study shows that patients with an inferior axis during VT, especially if they have ischaemic heart disease, are much less likely to have late potentials detected in sinus rhythm. This suggests that the site of origin of VT, whether superior or inferior, is important in determining the presence of late potentials.

Relative relevance of right and left ventricular biopsies in patients with ventricular tachycardia and clinically normal hearts

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A proportion of patients (10–15%) with ventricular tachycardia (VT) have clinically normal hearts. It has been suggested that endomyocardial biopsy may help to identify the underlying pathological process in such patients. Although right ventricular (RV) and left ventricular (LV) biopsies are usually performed, both procedures are associated with an unmeasurable risk. We have examined the relative relevance of performing RV and LV biopsies in patients with VT and clinically normal hearts. Twenty two patients (15 men, median age 45 years (range 19–70)) with documented VT were studied. The results of a chest *x* ray film, the QTc interval, left ventricular wall motion from angiography, and coronary arteries were normal in all patients. The configuration of the clinical VT was left bundle branch block pattern in 16 patients, right bundle branch block pattern in four, multiform in one, and indeterminate in one. Biopsy specimens were obtained by means of a Cordis bioptome, and an attempt was made to obtain three specimens from each ventricle. They were reviewed by a pathologist unaware of the configuration of the VT. The average number of biopsies was 2·6 from the right and 2·7 from the left ventricle. Nine patients (40%) showed abnormalities in the RV biopsy specimens, seven of the nine also showing abnormalities in the LV biopsy specimens No patient showed abnormalities in the LV biopsy specimen alone. The pathological findings from light microscopy were non-specific and included endocardial thickening; subendocardial interstitial and perivascular fibrosis; and cellular hypertrophy, atrophy, and vacuolation. Of the four patients with RBBB configuration of VT, three showed no abnormality in both biopsy specimens, and one showed abnormalities in both RV and LV biopsy specimens.

We conclude that a substantial proportion (40%) of patients with VT and clinically normal hearts show abnormalities in endomyocardial biopsy specimens and that LV biopsy in this group of patients confers little more information than that which can be obtained from RV biopsy.

Preoperative and intraoperative colour flow mapping in the definition of high velocity continuous shunting in the heart

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Continuous high velocity intracardiac shunting of blood is a comparatively rare finding in cardiology. Physical examination, duplex scanning, and angiography are all likely to give suboptimal information in such cases. Potentially, colour flow mapping (CFM) can determine the origin and extension of such a disturbance of flow by encoding turbulence, thus providing optimal diagnostic information in these complex lesions. Eighteen patients (seven ventricular septal defect/aortic regurgitation; five acquired Gerbode defects; two coronary sinus fistulas; four coronary artery/right heart communications) were studied. Seventeen patients had correlative angiography and 12 had had subsequent surgical confirmation of the defect. Cross sectional echocardiography alone showed the morphology in only seven patients. Continuous wave Doppler recorded high velocity continuous flow in all 18. Pulsed Doppler subsequently failed to predict the exact nature of the intracardiac shunt in nine patients. In contrast, CFM correctly defined the nature of the complex flow disturbance in all 18 patients (multilevel shunts being clearly shown in 13 patients in whom this was present). Angiography failed to adequately define the precise nature of the shunt in nine out of seventeen patients, being notably poor in distinguishing ventricular septal defect/aortic regurgitation from coronary sinus fistulas. Of the 12 patients undergoing corrective surgery, five had intraoperative CFM studies carried out to confirm the repair of the defect. In every patient surgical repair was shown to be effective by the absence of a significant residual flow disturbance.

We conclude that CFM is the investigative technique of choice in defining complex high velocity continuous intracardiac shunts and for the intraoperative assessment of their repair.

Improved ultrasound diagnosis of coarctation with colour Doppler flow mapping

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A duplex echo/Doppler system with colour Doppler flow mapping (CDFM) (Vingmed CFM 500) was used to determine the site and nature of the lesion in a consecutive series of 26 patients (seven newborns, four older infants, 15 older children) who presented with coarctation of the aorta and were being referred for operation. The site was clearly shown in 10 of the 11 infants but in only eight of the 15 older patients. CDFM showed increased velocity at the site of the coarctation in 24 of the 26 patients. In patients aged less than 1 week the increased velocity was usually from flow into the descending aorta through the ductus and not the coarctation site; in patients in whom the coarctation had already been shown CDFM confirmed the site; and in four of the most recent patients, in whom coarctation was not clearly shown, the superimposition of the colour display on the ultrasonographic image allowed the position and nature of the lesion to be appreciated and surgery to be undertaken without catheterisation.

CDFM adds considerably to the diagnostic capability of ultrasonography in coarctation of the aorta and obviates the need for angiography in many patients in whom imaging echocardiography fails to delineate the exact site and nature of the lesion.

Indium-111 labelled monoclonal antimyosin antibody for the localisation of transmural myocardial infarction

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The role of indium-111 labelled monoclonal antimyosin antibody antigen (AMA) binding fragment in localising myocardial necrosis was assessed in 13 patients with transmural myocardial infarction, eight of whom had received intravenous streptokinase. AMA was injected within 48 hours after the onset of chest pain. Images were obtained at 24 and 48 hours in three projections, and uptake of AMA was graded in intensity (0–4) by two independent observers. In all patients the images correlated with the site of Q waves on the electrocardiogram. Four images showed more widespread myocardial necrosis than indicated on the electrocardiogram. Eleven images showed no change in extent or intensity between 24 and 48 hours. Three "doughnut" images occurred with anterior myocardial infarction. The eight patients who received streptokinase (one million units intravenously) within 4 hours of the onset of pain nevertheless developed transmural myocardial infarction by electrocardiographic criteria. The image grade for those receiving streptokinase (mean 3·1 (SD 0·6) *v* 2·2 (0 4); $p < 0·05$) was greater than for those who did not. In a further five patients with chest pain, normal cardiac enzyme activities, and normal results from serial electrocardiograms the AMA images were negative. There were no adverse effects from injection of AMA.

In conclusion, AMA is an effective agent for localising myocardial infarction and in some patients indicates the presence of myocardial necrosis beyond the electrocardiographic changes. In those patients with a myocardial infarction despite receiving streptokinase the areas of myocardial necrosis produced more intense uptake of AMA. AMA images were clearly interpretable and provided a new way of assessing the site and extent of myocardial infarction.

Magnetic resonance imaging of coarctation of the aorta in infants

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The aortic arch was studied in eight infants (aged 5 days to 10 months) with coarctation of the aorta by magnetic resonance imaging. A 1·5 Tesla, high field strength, imaging system was used. Infants were positioned inside the adult head coil and multiple, simultaneous, 5 mm thick sections were acquired, which were gated by the electrocardiogram. A spin echo sequence was used. The imaging plane was, if necessary, oblique to standard planes of the body. Imaging was successful in every infant. Sedation with chloral hydrate was required in most of the infants. The area of narrowing was imaged in at least two, and usually three, planes in each infant. The relation of the coarctation to the left, or in one infant the right, subclavian artery was clearly shown, as was the aortic isthmus. All patients have subsequently undergone operative correction and the diagnosis confirmed. In a further four infants coarctation was suspected clinically and not excluded by cross sectional and Doppler echocardiography, but it was excluding by magnetic resonance imaging.

Magnetic resonance imaging is an important advance in the non-invasive imaging of aortic coarctation.

Acute effects of disopyramide, mexiletine, and flecainide in patients with impaired ventricular function assessed by nuclear angiography

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Antiarrhythmic drugs may precipitate cardiac failure in patients with severely compromised ventricular function. Many patients with arrhythmias have moderately reduced cardiac function. To assess the acute effects of class 1 antiarrhythmic drugs on cardiac function in patients with impaired left ventricular function we performed a double blind crossover study on nine men and one woman (mean age 57 years). All 10 of them had suffered myocardial infarction and arrhythmias and four had coronary artery bypass surgery. First pass radionuclide ventriculography was performed with either gold-195 m or technetium-99m before and after each drug. Disopyramide, mexiletine, and flecainide, 1·5 mg/kg, were given to each patient by intravenous infusion in random order on three separate occasions. Electrocardiograms and blood pressure were monitored throughout each study. Mean resting left ventricular ejection fraction (LVEF) was 37·0 (7·7) (range 27–48%). After disopyramide mean LVEF was reduced to 29·0 (7·2) ($p < 0.01$ compared with control); after mexiletine it was 33·3 (7·4) ($p < 0.05$) and after flecainide 31·6 (9·6 ($p < 0.025$). In the three patients with initial LVEF values of less than 30% the fall in LVEF was similar in magnitude after each drug. No drug had any significant effect on heart rate or blood pressure, and no patient developed overt heart failure. Mean serum concentrations of the drugs were disopyramide, 3·3 (0·7) mg/l; flecainide, 288 (132) µg/l; and mexiletine, 0·31 (0·29) mg/l.

Thus disopyramide and flecainide produce a similar reduction in resting LVEF values, whereas mexiletine has a significant but less pronounced effect with the same dose.

Can pulsed Doppler replace direct measurement of left ventricular end diastolic pressure?

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It has been claimed that simple measurements from pulsed Doppler recordings of left ventricular (LV) diastolic filling allow accurate and reliable estimates of left ventricular end diastolic pressure (LVEDP). This has important implications for acute coronary care, where decisions about treatment are often based on indirect pressure measurements. Simultaneous pulsed Doppler recordings of left ventricular pressure and diastolic inflow velocities were made in 32 patients with ischaemic heart disease. A multichannel recorder provided superimposed pressure, pulsed Doppler, electrocardiogram, and phonocardiogram traces, which allowed accurate timing and unambiguous identification of the events in each diastolic period. Micromanometer tipped catheters were initially used to calibrate the fluid filled pressure recording system. The range of LVEDP was 7–25 mm Hg. Computer assisted analysis of the Doppler flow patterns showed no correlation between the early (E) or late (A) diastolic flow velocity peaks or the E to A ratio (range 0·27–1·9) with the simultaneously recorded LVEDP. A weak positive correlation was found, however, between the mean deceleration from the peak initial velocity and the LVEDP ($r = 0.51$). Although characteristic abnormalities of left ventricular filling are detected by pulsed Doppler recording in ischaemic heart disease, they do not relate in a simple quantifiable way to LVEDP, which in itself correlates poorly with other indices of impaired ventricular function.

Pulsed Doppler recording of left ventricular filling as an isolated measurement does not provide a clinically useful alternative to direct pressure measurement in patients with ischaemic heart disease.

Follow up of patients after balloon dilatation of the aortic valve

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The long term outcome of balloon dilatation of the aortic valve (BAV) for aortic stenosis is uncertain, the development of symptomatic restenosis being a significant hazard. We followed up nine patients in whom BAV had been performed for relief of severe aortic stenosis for up to one year (mean nine months) using Doppler velocity measurements to assess aortic valve gradient. All patients had acquired aortic stenosis. Two patients had bicuspid aortic valve, one rheumatic aortic stenosis, and six senile calcific aortic stenosis. Mean transvalvar gradient at BAV was reduced from 80 mm Hg (range 50–120) to 51 mm Hg (range 20–70). Non-invasive follow up assessment of aortic gradient was made at six weeks and repeated at up to 12 months after BAV. Mean gradient at six weeks was 46 mm Hg (range 30–70) and at six months 50 mm Hg (range 35–80). Before BAV all patients were in New York Heart Association (NYHA) class III or IV. After BAV all patients reported improvement in symptoms with improvement in the NYHA class from IV to II in two patients, from III to II in three, and from II to I in four. Symptomatic improvement was sustained at follow up, but one patient deteriorated from class II to III.

We conclude that BAV, although primarily a palliative procedure in patients with critical aortic stenosis and unacceptable surgical risk, offers the prospect of sustained benefit in this group.

Controlled clinical trial of prednisolone in treatment of 240 patients with tuberculous pericardial effusion

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Tuberculous pericarditis is common in Transkei. To assess the effect of steroids as an adjunct to anti-TB treatment in pericardial effusion 240 patients with active effusion were randomised. All received the same six months course of anti-TB treatment. Those willing and suitable were randomised either to open drainage on admission or to closed pericardiocentesis as required, which was also performed as necessary in those unsuitable for open drainage. All patients were allocated to receive either prednisolone or matching placebo for the first 11 weeks of treatment. *Mycobacterium tuberculosis* was cultured from pericardial fluid in 57% of 188 patients, and characteristic histology was present in biopsy specimens of 72% of 33 patients. As assessed at 24 months, complete drainage on admission abolished the need for subsequent pericardiocentesis ($p < 0.01$) but did not diminish the risk of death or the need for subsequent pericardectomy for constriction. Among patients who did not have drainage on admission, two out of 76 (3%) given steroids, died of pericarditis compared with 10 out of 74 (14%) given placebo ($p < 0.04$); six (8%) and eight (11%) required pericardectomy, six (8%) and 17 (23%, $p < 0.02$) pericardiocentesis, and one (1%) and six (8%) open surgical drainage respectively. Open drainage on admission did not influence favourable state at 24 months, but 73 of the 76 (96%) patients given steroids had a favourable status compared with 62 (84%) given placebo ($p < 0.03$).

It is therefore recommended that in the absence of specific contraindication, anti-TB treatment should be supplemented initially by corticosteroids in the treatment of tuberculous pericardial effusion.

Captopril has a direct negative inotropic effect on isolated myocardium

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Angiotensin converting enzyme inhibitors (ACE) have been successful in the treatment of heart failure and are under investigation for use in myocardial infarction. Not all the actions of ACE inhibitors can be explained by their effect on circulating angiotensin II. Isolated strips of human right atrial muscle (H), obtained from patients undergoing cardiopulmonary bypass surgery, and guinea pig papillary muscles (GP) were mounted to contract isometrically at 1 Hz in physiological solution at 37°C. These were exposed to incremental doses of captopril of 100–800 ng/ml. A dose related negative inotropic action was detected (isometric tension with 800 ng captopril as proportion of control in H, 54 (14)% (n = 5); GP, 48 (12)% (n = 7)). The negative inotropic effects of 800 ng captopril were attenuated by 2·5 μM adrenaline (H, 62 (20)% (n = 3); GP, 72 (12)% (n = 5)). In both human and animal muscles atenolol (2 μg/ml) did not affect the negative inotropic action of captopril. A considerable effect on the recirculation fraction was observed when captopril was added to muscles superfused with adrenaline, which suggested an antiadrenergic effect. The recirculation fraction reflects myocardial inotropic state and is consistently increased by adrenaline (H, 0·63 (0·11) to 0·98 (0·21) (n = 3); GP, 0·46 (0·13) to 0·94 (0·30) (n = 5)). At the lowest doses of captopril investigated (100 ng/ml) the increase in the recirculation fraction produced by adrenaline was reversed (H, 0·56 (0·10); GP, 0·67 (0·14)).

These results show that captopril has a direct, non-beta receptor mediated antiadrenergic effect on human myocardium. The mechanism of this action remains to be explained.

Analysis of left ventricular function during follow up after intravenous streptokinase treatment of myocardial infarction

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Thrombolytic treatment during early acute myocardial infarction results in an early improvement in left ventricular function. In this study the long term effects of thrombolysis on left ventricular function were examined. Serial measurements of cardiac function were made on 64 patients treated with streptokinase (1·5 million units intravenously). Two groups of patients were followed up. Group 1 comprised 45 patients who received standard medical treatment after thrombolysis: twenty eight had an open and 17 a closed infarct related coronary artery at postinfarct angiography. Baseline and follow up radionuclide ventriculograms were examined at a mean 2·4 weeks and 11 9 months after treatment, respectively. Patients with anterior infarction and an open artery had a better baseline ejection fraction in the region of the infarct than those with a closed artery (34·1% (SD13) *v* 24 6% (10)). This initial benefit was lost at follow up (29·9% (10) *v* 30·7% (14)). No difference in regional ejection fraction was observed in patients with inferior infarction. Group 2 consisted of 19 patients who had successful reperfusion followed by percutaneous transluminal coronary angioplasty to a lesion of the infarct artery (mean stenosis 71·5% (7)). Contrast ventriculography was performed at baseline (6·4 (2) days) and follow up (16·7 (6) months) to evaluate a regional wall motion index. In 10 patients with anterior infarction regional akinesis decreased from 76·3 (84) to 34·3 (68) at follow up. No decrease in akinesis was seen with inferior infarction.

These data suggest that coronary reperfusion produces its main functional benefit in patients with anterior infarction. This improvement is maintained during follow up in patients who receive percutaneous transluminal coronary angioplasty but may be lost in patients who are followed by conventional medical treatment.

Balloon dilatation for pulmonary stenosis in older patients

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Percutaneous balloon dilatation of the pulmonary valve (PBPV) was performed on four older patients (three men, age range 56–70 years) with congenital pulmonary valve stenosis. All patients presented with dyspnoea (New York Heart Association grade III), including one patient with cardiac tamponade from a pericardial effusion which was relieved before PBPV. All patients had pulmonary systolic murmurs. Two patients also had ostium secundum atrial septal defects, and one had a membranous ventricular septal defect, although no shunts were shown on oximetry. PBPV was performed with a single 18 mm or 20 mm balloon and was well tolerated and free of complications. The transvalvar gradient fell from a mean (SD) of 79 (14 1) to 25 (10·8) mm Hg ($p < 0·01$). At three months all patients were symptom free and the mean transvalvar gradient was 28 (11·5) mm Hg. No increased shunt was shown by oximetry in those patients with septal defects. One patient was thought to have restenosed and underwent repeat PBPV. On review he showed infundibular stenosis with a gradient of 60 mm Hg across the right ventricular body to pulmonary artery but a transvalvar gradient of only 30 mm Hg, which had not improved by repeat PBPV.

PBPV is a well tolerated and effective treatment for pulmonary valve stenosis even in older patients and avoids the necessity for thoractomy. Infundibular stenosis should be excluded before the technique is performed.

Long sheath technique for percutaneous balloon dilatation of the aortic valve

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Anterograde percutaneous balloon dilatation of the aortic valve is conventionally performed without the aid of an intra-arterial sheath. The procedure is time consuming if multiple balloons are used and is associated with a significant rate of complications in peripheral vessels. We assessed the use of a new 100 cm 16·5 French sheath designed specifically for use with aortic balloon dilatations in nine consecutive patients and compared the results with those obtained by the conventional technique in the previous 18 consecutive patients. With the long sheath technique the procedure was shorter; mean duration 113 minutes *v* 211 minutes ($p < 0{\cdot}05$). The sheath was able to accommodate the largest balloon sizes (3 × 12 mm), and the balloons could be positioned with ease. In addition, the sheath was able to effectively splint the balloon in the valve orifice during inflation, avoiding the potentially dangerous to and fro motion. There were no fundamental differences in the haemodynamic results between the two groups. In the 18 patients in whom the conventional technique was performed, three required operative interventions for complications at the puncture site (two for the repair of pseudoaneurysms and one to allow removal of a balloon remnant) and two additional patients required blood transfusions for bleeding at the puncture site. There was no vascular complications in the long sheath group.

These preliminary results suggest that the long sheath is a valuable aid to percutaneous balloon dilatation of the aortic valve in that it reduces both the time of the procedure and the rate of complications in peripheral arteries.

Preparation of human saphenous vein for coronary artery bypass grafting impairs its capacity to release endothelium derived relaxing factor

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Intraoperative damage to saphenous vein grafts may contribute to both their early and late occlusion, and platelet activation may be involved in both processes. We investigated whether routine surgical preparation of saphenous vein led to impaired release of endothelium derived relaxing factor (EDRF), which would favour adhesion and activation of platelets. Veins were perfused at 23°C at 2 ml/min and bradykinin (10^{-6}M) stimulated release of EDRF into the perfusate was measured by its ability to relax a preconstricted (5-hydroxytryptamine 3×10^{-6}M) de-endothelialised porcine coronary artery. The maximum relaxation (expressed as a percentage of preconstricted tone) induced by stimulated release of EDRF was 60 (SEM 15%) ($n = 5$) in freshly isolated vein obtained by a no touch technique as soon as possible after the first incision and stored in heparinised blood for up to 60 minutes. It was 19 (3%) ($n = 11$) in vein obtained at the end of the surgical procedure (surgically prepared vein) ($p < 0{\cdot}01$). Relaxation induced by EDRF from freshly isolated vein that had been stored for 80–160 minutes declined to 25 (5%) ($n = 6$), which was similar to that induced by EDRF from surgically prepared vein.

This study shows that routine surgical preparation reduced the capacity of the human saphenous vein to release EDRF. It also suggests that prolonged storage in heparinised blood may contribute to this inhibition.

Clinical experience with a minute ventilation sensing rate responsive pacemaker

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Minute ventilation is linerly related to oxygen consumption and is used as an indicator to determine the rate in rate responsive pacing. The Meta pacemaker (Teletronics) senses minute ventilation by measuring thoracic impedance with a standard intravenous bipolar pacing electrode. Programmable rate responsive variables include rate limits (50–180 beats/min) and slopes of rate response (1–60). This pacemaker was implanted in 11 patients (complete heart block in nine, sinoatrial disease in two) with a mean age of 59 (SD 14) years. Programming was achieved with the help of suggested slopes during a submaximal exercise test (range of slopes programmed, 16–25). Treadmill exercise with the Bruce protocol performed in the rate responsive mode showed improvement in the duration of exercise over fixed rate pacing (608 (177) *v* 450 (128) s; $p < 0·001$). Cardiac output measured by continuous wave Doppler was improved by 44 (20)%. Appropriate rate responses to different workloads such as walking at different speeds and slopes were achieved. Ascending four flights of stairs resulted in a higher rate response than that on descending (110 (24) *v* 77 (5); $p < 0·01$). With activities like walking, rate response occurred at 24 (16) s and half of the maximum rate was attained in 92 (30) s. Voluntary effects on respiratory pattern can affect the pacing rate: talking continuously during a three minute treadmill exercise attenuated the rate response (from 123 (26) to 96 (22) beats/min; $p < 0·001$) and coughing for one minute increased the pacing rate (87 (8) beats/min).

It is concluded that the Meta pacemaker improves exercise capacity and cardiac output during exercise and its rate response is related to workload. Voluntary interference modified the response but excessive rate acceleration was not encountered.

Absent baroreceptor response in haemodialysed patients with chronic renal failure and good ventricular function

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Both autonomic and left ventricular dysfunction have been postulated as the cause of the serious hypotension that is a frequent complication of haemodialysis (HD). In 10 patients with end stage chronic renal failure who were being maintained on HD blood pressure was monitored continuously by an intra-arterial ambulatory technique over 24 hours before HD and continuing during it. Autonomic function was tested with the Valsalva manoeuvre, and technetium-99m gated radionuclide ventriculography was performed at the beginning of the 24 hour recording to assess left ventricular function. On the day of dialysis the ejection fraction was measured immediately before HD and every 30 minutes during it. The day and night variations in blood pressure and heart rate were significantly reduced in nine of the patients with chronic renal failure (blood pressure 12/7 (8/6) mm Hg, heart rate 6 (4) beats/min) compared with a control population (blood pressure 36/28 (10/5) mm Hg, heart rate 23 (9) beats/min) and all 10 patients had a classic "square wave" response to the Valsalva manoeuvre. Despite these indications of baroreceptor failure, which are usually seen in patients with severe cardiac failure, all 10 patients had a normal or high resting ejection fraction (mean 66%, range 55–79%) and peak filling rate (mean 3·1 end diastolic volume, range 2·7 to 5·5). They experienced a progressive fall in blood pressure during HD (mean maximal fall 42/21 (15/11) mm Hg) but their heart rate rose little or not at all (4·5 (5) beats/min) despite the volume depletion and hypotension. Nor was there any significant fall in ejection fraction during dialysis.

These results suggest that hypotension during HD is caused by a failure of the baroreceptor response to volume depletion. There is, however, no evidence of left ventricular dysfunction due to a uraemic cardiomyopathy, as has been postulated.

Why is atrioventricular block an ominous prognostic sign in myocardial infarction?

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Atrioventricular block is associated with a higher short term mortality in acute myocardial infarction, but it is not certain if this effect is independent of other prognostic factors such as infarct size. We studied 705 successive patients admitted with a first Q wave myocardial infarction, of which half were anterior, to determine the factors predisposing towards atrioventricular block and the relation of block to subsequent mortality. Second or third degree block developed in 61 (8·8%) patients. It was commoner in inferior (12·4%) than anterior (4·9%) infarction. A multiple logistic regression identified three factors as being independently correlated with block: inferior infarction, older age, and higher peak creatinine kinase activities (all $p < 0·01$). Mortality was 9·3% in patients without block and 27·9% in those with block. Mortality was significantly higher in both anterior (47·0% *v* 11·8%) and inferior (20·4% *v* 6·7%) infarction. When age, peak creatinine kinase activity, infarct site, and block were analysed simultaneously as predictors of death block was a significant independent prognostic factor, as were age and site, whereas peak creatinine kinase activity was not associated with death independently of the other three factors. The relative risk of death, corrected for age and creatinine kinase activity, was 4·57 in anterior infarction and 4·5 in inferior infarction.

The relative increase in the risk of death associated with atrioventricular block is as large in inferior infarction as it is in anterior infarction. Its prognostic effect is independent of age and not due to its correlation with infarct size: even in a small inferior infarction block appears to be an ominous prognostic sign.

Importance of stress testing in apical hypertrophic cardiomyopathy

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Apical hypertrophic cardiomyopathy (AHC) is a subgroup of hypertrophic cardiomyopathy characterised principally by unremarkable physical examination and electrocardiographic changes that may simulate myocardial ischaemia or athlete's heart. We studied 20 patients (mean age 50 years, range 24–76; 13 men) with clinical and echocardiographic features of AHC. Six had giant negative T waves (more than 10 mm) whereas 14 had T wave inversion ranging from 3–8 mm. Time course patterns of ST segment and T wave changes that occur with angiographically normal epicardial coronary arteries were shown. In nine patients the ST segment depression and T wave inversion improved immediately after exercise and returned to the pre-exercise appearances 3–5 minutes after exercise. In another nine patients the ST and T wave changes worsened immediately after exercise but returned to control values 3–5 minutes after exercise. Neither of these time course patterns is compatible with ischaemia, but the former pattern is also encountered in athlete's heart. Coronary arteriography performed in 15 of the 18 patients yielded normal results. The remaining two patients showed a time course pattern associated with ischaemia in that the ST and T wave changes worsened immediately after exercise and remained abnormal for 10–12 minutes. Coronary angiography showed significant right coronary artery lesions in both patients.

We conclude that stress testing can differentiate AHC from ischaemia and that coronary artery disease associated with AHC may be detected. Evaluation of the postexercise time course patterns of ST segment and T wave changes will also differentiate athlete's heart from some cases of AHC.

Development of a current based defibrillator

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As current rather than energy is considered the more important factor in successful defibrillation we studied 37 consecutive patients (29 men, eight women; mean age 60 (range 41–81 years)) with 41 cardiac arrests (ventricular fibrillation) who received a first shock of 200 J and if required a second of 200 J and then 360 J delivered thereafter to assess peak current (Ip) at defibrillation. With self adhesive pregelled 12/12 cm pads in the anterior-anterior position a first shock of 200 J was successful in 33 of the 41 (81%) cardiac arrests and a first or second shock in 39 (95%) (mean Ip for successful defibrillation, 32 (SD 6·3) A (range 22–48); mean predicted transthoracic impedance (TTIp) 70 (SD 16) Ω (range 41–122 Ω)). We then developed an Ip based defibrillator in which a microprocessor uses TTIp and preprogrammed defibrillator characteristics to estimate the energy required to produce a preselected Ip for each patient. We studied a further 45 consecutive patients (30 men, 15 women; mean age 62 (range 19–81 years)) with 45 cardiac arrests where the first shock was 30 A and if unsuccessful the second shock was 30 A and then 40 A if required. For safety, manual charging to the energy required was used. Component tolerance and operator variability led to small variations in Ip. A first shock of 30 A was successful in 36 of the 45 (80%) cardiac arrests and a first or second shock was successful in 44 (98%) (mean Ip for successful defibrillation, 29 (SD 1·4) A (range 25–31); mean TTIp, 69 (SD 17) Ω (range 38–104); and mean energy per shock was 154 (SD 66) J (range 63–304)). Thus the mean energy per shock of 154 J delivered using an Ip system was significantly less than using 200 J ($p < 0{\cdot}001$) and the mean Ip per successful shock was also reduced (29 A *v* 32 A; $p < 0{\cdot}05$). First shock success, however, was not significantly different (80% *v* 81%).

Mechanisms for the early mortality reduction produced by β blockade in acute myocardial infarction

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For ISIS-1 Collaborative Group

In the First International Study of Infarct Survival (ISIS-1)[1] the mortality was 15% lower in the group randomised to receive atenolol in the early hours after the onset of suspected myocardial infarction than in the control group. An unexpected finding on retrospective analysis of the data was that this benefit was mainly confined to deaths during the first two days of treatment, there being little further divergence in the mortality of the two groups subsequently. To determine the mechanisms responsible for this reduction in mortality, the case notes of patients in the British Isles and Scandinavia who died during days 0–1 of the trial were scrutinised. Adequate records were available for 193 of the 217 patients. Of the 79 patients given atenolol who died, necropsy confirmed rupture in five; a further 15 had electromechanical dissociation, but no necropsy had been performed. Comparable figures for the 114 patients in the control group were 17 and 37. As rupture was probably responsible for most of the cases of electromechanical dissociation the difference in fatality in the two groups can largely be explained by this mechanism. Additional findings included a slightly higher frequency of fatal ventricular fibrillation and aortic dissection in the control group, and of bradycardia and asystole in the atenolol group.

Limitation of infarct size and the prevention of reinfarction do not seem to have played a part in the reduced mortality

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[1] ISIS-1 report *Lancet* 1986,ii 57–66.

Changes in neutrophil activation and free radical activity after thrombolysis for myocardial infarction in man

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Thrombolytic treatment after myocardial infarction is widely practised but reperfusion injury, with free radical production and amplification of the inflammatory response, remains a possibility. We previously showed increased free radical activity (non-peroxide diene conjugate of linoleic acid (octadecadienoic acid)) and neutrophil activation with release of netrophil elastase in myocardial infarction. We have since measured these activities sequentially over 48 hours in 16 patients with acute infarction: eight who were given intravenous thrombolytic treatment (age 52·5 (13·4) years) and eight who were treated conventionally (age 57·9 (11·9) years). Octadecadienoic acid concentration increased in the thrombolytic (34·83 (4·46) μmol/l; $p < 0·001$) and non-thrombolytic (30·79 (6·0) μmol/l; $p < 0·01$) groups compared with normal values (19·45 (1·09) and fell over the 48 hours. There was no difference between the two groups. Neutrophil elastase values increased above normal values (21·2 (2·0) ng/ml) in the thrombolytic (49·58 (8·41); $p < 0·001$) and non-thrombolytic (37·25 (9·76) ng/ml; $p < 0·02$) groups. The non-thrombolytic group showed a biphasic increase in neutrophil elastase values with a significant second peak at 40 hours (55·01 (8·89) ng/ml) that was not seen in the treated group (32·43 (3·72) ng/ml; $p < 0·05$). The inflammatory response was imaged by indium-111 labelled autologous neutrophils in a subgroup of these patients and seemed attenuated in the group receiving thrombolysis.

Thrombolytic treatment within four hours after onset of symptoms is not associated with greater free radical induced damage and abolishes neutrophil activation in the second day after myocardial infarction, when neutrophils are normally present in the infarcted area. Reperfusion injury may therefore be a theoretical rather than an actual phenomenon.

Early intervention in myocardial infarction with streptokinase at home and in accident and emergency department

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The beneficial effect of intravenous streptokinase in acute myocardial infarction decreases with the delay between the onset of symptoms and intervention. We report our experience of streptokinase given at home, in the accident and emergency department, and in hospital (CCU). Between August 1985 and April 1986, 38 patients in the CCU received intravenous streptokinase within four hours according to conventional criteria. Thereafter unit policy was to give intravenous streptokinase at home or in the accident and emergency department when practicable. Since then, of 138 admissions, 43% received streptokinase at home, 24% in the accident and emergency department, and 33% in the CCU. Complications outside hospital were few: two patients had ventricular fibrillation, four transient hypotension, and one transient asytole; one patient bled from the forehead and another died in shock. Of patients given intravenous streptokinase outside hospital, two had ventricular fibrillation and one haematemesis and one patient developed a saddle embolus in the CCU. The mean delay for patients given intravenous streptokinase at home was 104·5 (SE 7·2) minutes, in the accident and emergency department 127·7 (8·9) minutes, and in the CCU 165·4 (8·6) minutes (all differences significant). Seven patients given intravenous streptokinase at home and three in the accident and emergency department would have been ineligible on delay criteria for such treatment in the CCU.

Intravenous streptokinase given at home or in the accident and emergency department is safe, reduces delay to intervention by up to one hour, and allows the treatment to be given to more patients.

Kinetic changes in coagulation, fibrinolysis, and plasma viscosity associated with coronary artery reperfusion with tissue plasminogen activator in acute myocardial infarction

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Twenty one patients (15 men, six women, age range 38–68) with acute myocardial infarction (< 4 hours; 13 anterior, eight inferior) received either placebo ($n = 11$) or 100 mg tissue plasminogen activator (rtPA) ($n = 10$) in a double blind randomised design. Serial samples were taken for profiles of creatine kinase (CK) release and at 0, 30, 45, 60, 90, 120, 180, and 240 minutes to measure serial changes in coagulation, viscosity, and fibrinolysis (with and without monoclonal antibody to rtPA (Ab). An early (12 hours) peak in CK activity suggestive of reperfusion was seen in eight of the ten patients receiving rtPA and in only one of the 11 receiving placebo; mean values (SEM) 2852 (1246) iu/l (rtPA), 1590 (1087) placebo at 12 hours and 2404 (1268) (rtPA), 2108 (1045) placebo at 24 hours. Fibrinogen concentration fell within 30 minutes from 2·8 (0·3) g/l to a nadir at 45 mins of 1·1 (0·2) g/l ($p < 0{\cdot}01$) and plasminogen values fell from 98·7% to 47% (8) at 30 minutes. The addition of Ab inhibited in vitro activity reducing the fibrinogen fall from 3·2 (0·3) ($t = 0$) to 2·4 (0·4) at 30 minutes ($p < 0{\cdot}02$) and plasminogen from 47 (8) (rtPA) to 65 (9) (Ab) at 30 mins ($p < 0{\cdot}05$). Plasma viscosity fell from 1·14 (0·02) m pasq.s to 1·09 (0·01) ($p < 0{\cdot}02$) and was sustained for four hours. There were no changes in the placebo group. Fibrin clot lysis (D-dimer) showed initial similar values (99 (4·5) mg/ml (rtPA), 114 (24) placebo; NS) but rose in the active group at 30 minutes to 687 (166) ($p < 0{\cdot}01$), which was sustained for four hours These results show that rtPA has a rapid onset of activity, a sustained firinolytic effect, and decreased plasma viscosity and is associated with an early high peak of CK release. Accurate measurement of in vivo fibrinolytic activity is obtained by the addition of Ab to blood samples for assay.

Does chronic pre-infarction angina affect in hospital outcome in patients with a first acute coronary event?

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Several studies have reported an adverse short term prognosis after myocardial infarction associated with previous chronic angina of effort. To determine if this effect was independent of other prognostic factors we studied 955 consecutive patients of all ages, of whom 329 (34·5%) were women, 750 (78 5%) were admitted to coronary care with a first myocardial infarction, and 205 (21·5%) were admitted to coronary care with an episode of unstable angina. A history of angina of effort dating at least three months before admission was present in 211 (22 1%) patients. These patients with previous angina were an average of 4·2 years older than those with no such history ($p < 0{\cdot}001$). They had higher cholesterol concentrations ($p = 0{\cdot}016$) and did not smoke as much ($p < 0\ 001$). The two groups did not differ in either the occurrence of hypertension or high density lipoprotein cholesterol concentrations. The mortality in hospital of patients with previous angina was 12 3% whereas that of patients without previous angina was 7·7% ($p = 0\ 036$). Patients with previous angina also had a higher rate of heart failure and cardiogenic shock (28·9% *v* 22·2%; $p < 0{\cdot}041$). When multiple logistic regression was used to correct for the difference in age between the two groups previous angina correlated neither with mortality ($p < 0{\cdot}289$) nor with complications ($p = 0\ 432$). Patients with previous angina had smaller infarctions, as assessed by peak cardiac enzyme activities ($p = 0{\cdot}013$), which may reflect better collateral circulation.

We conclude that the reported adverse effect of previous angina on early prognosis after an acute coronary event results from the difference in age between those with and without angina.

Thrombolysis in acute myocardial infarction: why the delay?

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Interest in early thrombolysis for acute myocardial infarction (AMI) led us to conduct a prospective audit of delays occurring during the management of emergency patients with chest pain both in the accident and emergency department of this teaching hospital and during transfer to the cardiac care unit (CCU). Over a period of 100 days 235 patients attended the accident and emergency department with chest pain, but we excluded three who discharged themselves from the department and 45 in whom neither the time at which the doctor first saw them nor the time of leaving the department were recorded in the boxes available on the casualty card. As all intervals fell on a skewed distribution medians and ranges are given. The median delay between arrival at the accident and emergency department and first seeing a doctor was 32 (0–215) minutes for the 155 patients for whom this measure was available. In 49 of these patients who were brought by ambulance the delay was 17 (0–175) minutes, while in 18 who were later transferred to the CCU it was 11 (0–75) minutes. The median stay in the accident and emergency department (difference between arrival and departure times) was 78 (19–510) minutes for the 126 patients in whom this measure was available. In 22 patients who were transferred from the accident and emergency department to the CCU the median stay was also 78 (25–422) minutes. The median stay was related to the number of investigations performed (no electrocardiography or chest *x* ray, 48 (19–133) minutes (n = 21); both electrocardiography and chest *x* ray, 91 (33–510) minutes (n = 10), and to different doctors (medians 66 to 91 minutes). In a second study the median differences between the arrival of 29 consecutive patients with AMI or unstable angina at the accident and emergency department and their admission to the CCU was 115 (42–406) minutes.

These timings raise questions about the management of patients with AMI in accident and emergency departments, the role of the CCU in early management of AMI, and the feasibility of early thrombolysis.

Out of hospital resuscitation in Brighton 1981–6

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The resuscitation ambulances in Brighton practise a system of immediate care that depends wholly on ambulance crews who have received extended training in a range of disciplines. From January 1981 to December 1986, 143 patients were successfully resuscitated from cardiac arrest out of hospital and survived to be discharged alive. Of these, 125 (87%) were victims of heart attacks or aborted sudden cardiac death. Seventeen patients (12%) suffered a primary respiratory arrest, which was secondary to acute asthma in eight, pulmonary oedema in one, overdose in five, respiratory obstruction in two, and hanging in one. Hypovolaemia after having been stabbed was the cause of circulatory collapse in one patient. In 85 patients (59%) cardiorespiratory arrest preceded the arrival of the ambulance. Eighty three patients (58%) recovered after only basic life support manoeuvres and defibrillation. In 60 patients (42%) additional advanced skills—namely, endotracheal intubation (52) and administration of drugs (eight)—were judged instrumental in achieving a successful outcome.

Instruction in basic life support and defibrillation deserves priority in extended training of ambulance crews because it can be achieved readily and saves lives. But many attempted resuscitations can be successful after prolonged cardiorespiratory arrest only when other techniques of advanced life support are available. Multidisciplinary training for ambulance crews is valuable and should be provided whenever possible.

Do all patients receiving intravenous thrombolytic treatment require aggressive invasive management?

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There is uncertainty about the need for aggressive investigation and management of patients with myocardial infarction (MI) after fibrinolytic treatment. Early invasive intervention is difficult in hospital without catheter laboratory facilities. Between August 1985 and July 1987, 170 patients with suspected MI were treated with intravenous streptokinase by this hospital's coronary care unit backed by a mobile unit. Catheterisation after treatment with streptokinase was performed acutely only on recurrence of chest pain or electively, depending on the patient's clinical and follow up treadmill electrocardiographic results. Medical treatment included long term aspirin and beta blockade unless these were contraindicated. Criteria for intravenous streptokinase included a delay from the onset of pain of four hours or less and ST segment elevation or considerable ST segment depression. Conventional contraindications applied. Q waves and clinical heart failure were not contraindications. Coronary arteriography was carried out in 15% of patients, usually electively after the first outpatient review. Three per cent of patients had percutaneous transluminal coronary angioplasty and 3% had coronary artery bypass graft. Some patients are currently awaiting either percutaneous transluminal coronary angioplasty or coronary artery bypass graft. The mortality at mean follow up over 12 months was 4·7%, which is lower than expected from coronary prognostic index.

Comparison with other centres advocating early invasive investigation with view to early percutaneous transluminal coronary angioplasty or coronary artery bypass graft is difficult as comparability of patients is impossible to establish. Our results suggest, however, that intravenous streptokinase followed by a conservative investigational approach is justified. Fibrinolytic treatment is appropriate in a district general hospital without catheter facilities.

Balloon dilatation of the aortic valve for congenital aortic stenosis beyond infancy

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Experience in infants suggests that balloon dilatation of the aortic valve (BAV) can provide effective relief of aortic stenosis after the neonatal period. We attempted BAV as the primary procedure in 29 consecutive children beyond infancy (aged 16 months to 17 years, median 7 years) from June 1985 to November 1987. On echocardiography, the aortic valve appeared to have three cusps in 20 (70%) patients, two cusps in eight (27%), and no commissures in one (3%). The aortic valve was crossed in all but one patient. In 28 patients the mean peak to peak systolic pressure gradients decreased from 72 (SD 31) to 31 (20) mm Hg ($p < 0·001$). The reduction in gradient was 57%. New aortic regurgitation occurred in seven patients (grade I in six, grade II in one) and was exacerbated (from grade I to II) in two out of six patients with pre-existing mild aortic regurgitation. There were no other complications apart from femoral artery occlusion in one (3%) patient who required treatment with intravenous streptokinase. In 10 patients who were restudied three to 14 months later there was no significant change in gradient from that immediately after BAV (48 (16) *v* 48 (22) mm Hg). The two patients with the highest residual gradient after BAV showed substantial improvement at restudy (70 to 42 mm Hg and, 70 to 40 mm Hg), while the patent with the unicusp aortic valve showed an increase in gradient from 37 to 99 mm Hg over nine months and required aortic root replacement. Surgical valvotomy was performed in the child in whom the aortic valve could not be crossed, but no other patients underwent aortic valve operation

The short term results of BAV suggest that it offers safe alternative palliation to valvotomy.

Cavopulmonary anastomosis with preservation of pulmonary artery continuity in patients with univentricular heart

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Since 1967 the condition of 27 patients with univentricular heart (UVH) and severely reduced pulmonary blood flow has been palliated by constructing a side to side cavopulmonary anastomosis (CPA) with ligation of the superior vena cava at the right atrial junction. The continuity of the pulmonary artery was thus preserved. There were 17 patients with tricuspid atresia (group A, mean age 32 months, range 16 days–108 months) and 10 patients with other complicated UVH (group B; mean age 48 months, range 5 weeks–180 months). In two patients with non-communicating left and right superior vena cavas bilateral CPAs were performed. A further two patients had azygos continuation of the inferior vena cava. There was one death related to a procedure in a 5 week old. Clinical improvement occurred in all survivors, and in 15 no further intervention was required (mean follow up 8 years, range 2–15). In 11 patients further surgery was performed because of increasing hypoxia in spite of angiographically proven shunt patency and low pulmonary artery pressure. There were three Fontan procedures, two peripheral arteriovenous, four Blalock-Taussig, and two aortopulmonary shunts.

CPA may have advantages over systemic to pulmonary artery shunts. Venous blood is directed to the lungs without increasing the volume load on the ventricle or significantly increasing pulmonary artery pressure. The anatomy of the pulmonary artery is preserved, which improves the anatomical scope for a later Fontan procedure. The results in some patients were so good that the Fontan operation was considered unnecessary.

Survival in complete transposition of the great arteries: a 10 year review

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Until recent years the standard management for the infant with uncomplicated ventriculoarterial discordance has been balloon atrial septostomy (BAS) followed by Mustard's or Senning's correction. In some centres an anatomical correction in the neonate is now preferred despite an increased operative mortality. In the light of this change in direction we reviewed our experience in Belfast. The records of 35 patients with uncomplicated ventriculoarterial discordance who presented from January 1978 to December 1987 were studied. All patients underwent BAS at 1–18 days (mean 5 days), which produced satisfactory palliation in 26 (74%). Six of these 26 patients (23%) died while awaiting corrective surgery. Fifteen patients were successfully corrected: 10 by Senning's and five by Mustard's procedure. There was no operative mortality, but two late deaths occurred among the patients treated with Mustard's procedure. Five infants currently await correction. In the nine patients (26%) with an unsatisfactory initial BAS, the procedure was repeated in five. Two underwent a Blalock-Hanlon septectomy and one an open septectomy, who did not survive the operation. Six had early correction (at less than 6 weeks of age): four by Senning's and one by Mustard's procedure. The remaining patient had an anatomic correction but did not survive. The mortality for the patients overall was 10 (28%). Seven (20%) died before corrective surgery with one death related to an open atrial septectomy and none directly related to BAS. There were 22 survivors of corrective surgery (8 aged less than 5 years), with no operative mortality for Mustard's or Senning's procedure irrespective of age, but a late mortality in two (9%).

In summary, in our experience atrial redirection for uncomplicated ventriculoarterial discordance carries negligible operative mortality. There is, however, a significant mortality before definitive repair despite apparently successful palliation by BAS.

Pathophysiology of atypical tamponade in infants undergoing cardiac operation

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Not presented

Fate of patients with transposition of the great arteries in the Republic of Ireland 1979–87

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All cases of suspected congenital heart disease in the Republic of Ireland are referred to this hospital. There were 104 patients with transposition of the great arteries (TGA) born during this period of eight years. Subgroups with associated patent ductus arteriosus (PDA), ventricular septal defect (VSD), left ventricular outflow obstruction (LVOTO), alone or in combination, were defined. The largest of these was isolated TGA (51%). The male to female ratio was 1·8:1, the mean birth weight was 3410 g (1800–4900 g), and the mean age at referral 5·3 days (0·2–84 days). Altogether 99 patients had balloon atrial septostomy (BAS) at a mean age of 5·9 days, 35 through the umbilical vein and 25 under echocardiographic guidance. One patient died during BAS. Other complications of BAS were infrequent (7%). After BAS and before definitive surgery complications included hypercyanotic spells, 13 patients (13%); cardiac failure, 11 (11%); and cerebrovascular accidents, four (4%). Six patients died before definitive surgery: one with profound hypoxia at 4 weeks, one after PDA ligation at 10 weeks, two with septicaemia at 5 and 12 months, one with CVA at 11 months, and one at home at 17 months. Palliative surgery was required in 10 patients (10%): Blalock-Taussig shunt in six (6%), pulmonary artery banding in three (3%), PDA ligation in two (2%). Eighty two patients had definitive surgery. The subgroup with isolated TGA had an operative mortality of 4 3%. The overall operative mortality was 19 5%. In the first half of the study period (1979–83) the operative mortality was 24% as compared with 7·5% for the second half (1984–87). There were three late deaths (3 6%). Fifty eight operative survivors were followed for a mean of 2 5 years after operation (mean 0 2–5·8 years). Forty six (75%) were in sinus rhythm. Ten patients (17%) were in nodal rhythm alone or alternate with sinus rhythm. None has required pacing. Four patients (7%) had residual hemiparesis and one (1·7%) motor developmental delay. Two patients (3·4%) have systemic ventricular failure. None has shown evidence clinically or at repeat cardiac catheterisation (17 patients) of pulmonary or systemic venous pathway obstruction.

This represents the first study of patients with TGA in the Republic of Ireland. These results compare favourably with other reported series.

Postnatal management of supraventricular arrhythmias diagnosed in utero

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Twenty two out of 23 children with supraventricular arrhythmias in utero (12 hydropic) had intrauterine antiarrhythmic treatment that was successful in 14 and partially successful in three. Eleven children (10 hydropic) required resuscitation at birth; four of nine infants had complications of prematurity. Postnatally, supraventricular tachycardia occurred in eight, atrial flutter in eight (two with atrial septal defects), and atrial tachycardia in two. Five children with arrhythmia control in utero remained in sinus rhythm from birth. Digoxin was administered within 48 hours of birth in 19 children and at 3 weeks in another. Three received additional antiarrhythmic agents (verapamil in two, propranolol in one). DC cardioversion was necessary in five. One premature child with partially controlled atrial flutter died. Pre-excitation was present on electrocardiography in three. Digoxin was later (16 months) successfully withdrawn in two of the eight with supraventricular tachycardia (mean follow up 52 months). Five of the six currently taking digoxin are aged less than 1 year; the other (aged 3) with a pre-excitation syndrome had recurrent arrhythmias for 15 months. It was possible to withdraw digoxin in four of the eight children with atrial flutter (mean age 8 months) with no recurrence on follow-up (mean 40 months). Atrial tachycardia was more resistant to treatment, requiring both amiodarone and digoxin in one child who later died of meningitis aged 23 months. Another with atrial tachycardia failed to respond to medical treatment.

We conclude that postnatal control of superventricular arrhythmias diagnosed in utero is achievable, often with digoxin alone, and treatment can later be withdrawn in most patients by the age of 1 year. The rarer atrial tachycardias are more resistant to treatment.

Magnetic resonance imaging of ventricular septal defects in infants

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Electrocardiogram gated cardiac magnetic resonance imaging was performed in 10 infants (aged 6 weeks to 4 months) with ventricular septal defects. A high field strength (1 5 Tesla) imaging system was used with the infant, sedated if necessary, placed in an adult head coil. A spin echo sequence was used, multiple, synchronous, 5 mm thick sections being acquired in various imaging planes. Sections that were related to the long and short axis of the heart were used. The angles of the imaging planes were chosen individually in each patient to show the anatomy of the ventricular septum optimally. Imaging was successful in every patient. Six patients had perimembranous defects, the relation of the defect to the central fibrous body being readily determined from the images. One patient had a doubly committed, juxta-arterial defect. The area of fibrous continuity between the arterial valves, which was roofing the defect, was clearly shown. Another patient had a bilateral subarterial infundibulum in association with the defect, which was excellently shown. Two further patients had muscular defects. In one of them the defects were multiple. In all patients the anatomy of the ventricular septal defects was more clearly shown in the magnetic resonance images than by cross sectional echocardiography or, in four patients, cineangiography.

Our early experience suggests that magnetic resonance imaging will become the optimum technique for imaging ventricular septal defects.

Paediatric supraventricular arrhythmias: age at presentation, nature, and treatment

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Of 97 children referred with supraventricular arrhythmias, 70 had paroxysmal re-entry supraventricular tachycardia (PRSVT), 25 of these had an overt pre-excitation syndrome (Wolff-Parkinson-White syndrome (WPW), 20 had atrial fibrillation or flutter (AF), and seven atrial tachycardia. Of the 70 with PRSVT, structural heart disease was present in twelve (17%). Twenty three (51%) without overt WPW presented before the age of 6 months and 14 (31%) between 7 and 12 years. Twelve (27%) received at least three antiarrhythmic drugs; electrophysiological studies were performed to aid treatment in 13 (29%); one child received an antitachycardia pacemaker and one operation. Of the 25 with overt WPW, 10 (40%) presented before the age of 6 months and 12 (48%) between 7 and 12 years. Ten (40%) of these received at least three antiarrhythmic drugs; electrophysiological studies were formed in 15 (60%), which led to one child receiving an antitachycardia pacemaker and two operation. Ten of the 20 children with AF (50%) had structural heart disease, and in 6 AF occurred post-operatively associated with sinus node dysfunction. Of the remaining 10, nine presented before 1 month of age. Arrhythmia control was obtained in 12 (60%) with one antiarrhythmic drug and three (15%) required no antiarrhythmic drugs; electrophysiological studies were performed in two (10%) and two received antitachycardia pacemakers. Two of the seven children with atrial tachycardia had cardiomyopathies and one child congenital heart disease; ages at presentation varied widely. Four children (57%) received at least three antiarrhythmic drugs, electrophysiological studies were performed in three (43%), one received an antitachycardia pacemaker, and one operation.

In conclusion, PRSVT was the most common paediatric supraventricular arrhythmia and had a bimodal age presentation. Half of those with AF have structural heart disease. Medical management achieved control in most, although surgery or a pacemaker was occasionally required for refractory arrhythmia.

Long term follow up after coronary thrombolysis in acute myocardial infarction

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Between 1982 and 1985 113 patients (mean age 55 years) who presented at a median time of 2·6 hours (range 0·5–6) after the onset of symptoms of acute myocardial infarction were treated with an intravenous or intracoronary thrombolytic agent. One hundred had angiographically proven coronary recanalisation. One hundred and five patients survived to leave hospital, and 100 of these have been followed up to the end of November 1987 (minimum follow up 23 months, median 35 months). A consistent follow up policy was adopted, consisting of early anticoagulation with heparin (controlled by the calcium thrombin time) followed by warfarin. Angioplasty or coronary grafting were used only when there was post-infarct angina or a strongly positive exercise test. Reinfarction (confirmed by electrocardiographic and enzyme criteria) occurred in nine hospital inpatients, seven of whom were not treated with anticoagulants at the time. Nine other patients sustained a myocardial infarction during the first year after treatment and four of them were treated with warfarin. After one year only two more patients had a myocardial infarction. Twenty six patients (25% of those alive at time of hospital discharge) had an intervention during the subsequent 24 months because of persistent or recurrent angina. Intervention was undertaken within three months of discharge in 13 cases. In hospital mortality was 7·1% and was due to pump failure in five cases and to cardiac rupture, papillary muscle rupture, and sudden death in one case each. A further six patients died during the first year—all these deaths were "sudden". Three of the late deaths were in patients in whom reperfusion had been unsuccessful.

Pacing termination of spontaneous ventricular tachycardia

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Pacing techniques to terminate ventricular tachycardia (VT) induced during electrophysiological testing are well documented but require specialised equipment. We attempted pacing termination of spontaneous VT in the coronary care unit with a standard external pulse generator with 3 × 3 rate multiplier. Temporary pacing lines were inserted on 27 occasions in 15 patients (13 men) aged 38–76. Twelve had previous myocardial infarction, one recent (48 h), and two had cardiomyopathy. There were 68 separate episodes of spontaneous VT. Intravenous antiarrhythmic treatment terminated VT in only seven (22%) of 32 attempts, while pacing termination was successful in 31 (54%) of 57 attempts. Underdrive and overdrive pacing were used when appropriate and were successful in 13 (34%) of 38 and 18 (46%) of 39 attempts respectively. Acceleration, with a subsequent need for DC cardioversion occurred on four occasions during pacing and once during catheter manipulation (9%).

The success rate of pacing termination of spontaneous VT at the bedside is similar to that obtained with induced VT in the laboratory. This technique minimises the need for repeated DC cardioversion or the use of multiple intravenous antiarrhythmic drugs.

Human defibrillation thresholds with biphasic waveforms and contoured epicardial patches

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Implantable defibillators are becoming established as important devices for the management of life threatening ventricular arrhythmias. Present devices are bulky because they require large batteries and capacitors; so reduction of energy requirements is an important goal. We studied the defibrillation threshold (DFT) with contoured large surface area epicardial patches (60 cm and 58 cm) in 21 patients (18 men, three women) undergoing coronary artery surgery. An incremental energy protocol was used in nine patients and a "searching" modified Bourland protocol in 12. The pulse consisted of a biphasic impulse (6·5 ms +ve/3·5 ms −ve), timed to discharge 10 seconds after the onset of induced ventricular fibrillation. Clinical details, left ventricular function, and coronary anatomy were evaluated and were correlated with the DFTs. The mean age was 58 years (range 46 to 71). Mean left ventricular ejection fraction was 59%. Eight had previous infarction, 16 were taking β blockers, and 16 were taking calcium blockers before operation. The mean DFT was 2·6 (2·3) (0·7 to 9·3) J, (174 (69) (96 to 357) V, with a mean measured impedance of 63 2 (14·6) (42·6 to 100 7) Ω. Sixteen patients had DFTs of <3 J, and 16 patients had DFTs of <175 V. There were no significant predictors of DFT based on clinical and anatomical details. Two patients with fatty hearts had notably higher DFTs but unremarkable impedances. There was no significant difference between the two different protocols.

Very low DFTs are possible if large contoured epicardial patches and biphasic pulses are used. DFTs were not significantly influenced by clinical and structural variables, except pericardial fat; none the less these patients did not have severely impaired left ventricular function. These finding have implications for optimising the design of implantable defibrillators.

Laser probe design: features of the optimum probe for coronary angioplasty

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Thermal angioplasty with a percutaneous laser probe (LP) is now used as an adjunct to balloon angioplasty in peripheral arteries. We evaluated techniques of delivering LP energy to coronary arteries by three different LPs in 11 perfused coronary arteries in seven intact cadaver hearts suspended in a water bath at 37°C. A guiding catheter was used for angiography, passage of the laser probe, and simultaneous perfusion with 60 ml/min during lasering. The most rigid LP (2·0 mm tip) used for peripheral angioplasty was unable to pass more than 2–3 cm into the major coronary vessels. A more flexible 1·5 mm LP with a guide wire through the tip could be passed to distal vessels but only by unacceptable displacement of the coronary arteries. Incorporation of the optical fibre into a catheter with a 2 cm floppy spiral metal coil proximal to the tip (1·7 mm) and a central guide wire channel permitted access to the distal vessels with less lateral distortion but also with reduced axial force that was necessary to advance the LP through atheromatous stenoses. Application of laser energy (10 W for 5–15 s) to the stationary probes resulted in lateral adherence to the vessel wall in 20/25 coronary segments. There was macroscopic charring of the vessels in 8/13 segments not perfused during lasering and 0/12 segments that were perfused ($p < 0{\cdot}05$). Three segments in which the vessel diameter to probe diameter ratio was <1·5:1 were perforated. Adherence and charring did not occur in any of the segments in which the vessel to probe ratio was >2·1:1.

Flexible, small diameter, LPs are most appropriate for coronary laser angioplasty because they give vessel to probe diameter ratios which reduces lateral damage while retaining sufficient strength to avoid their being welded to the artery wall as they are advanced through the vessel.

Comparative survival at twelve months of patients admitted by mobile coronary care unit and ordinary ambulance

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The mortality in an area served by a mobile intensive coronary care unit was compared with that in a similar neighbouring area without such a unit. Mortality was 13% less in the area with a mobile unit. After a mobile unit was established in the other area survival at three months and 12 months and coronary prognostic indices were compared in patients admitted to the district coronary care unit by ordinary ambulances and by the mobile intensive coronary care unit. Three hundred and forty three patients with 385 cardiac events entered the study (mean age 63 (19–89), 63% men and 37% women). The distribution of infarcts by type and site was similar in both admission transport groups ($\chi^2 = 2{\cdot}93$, df = 5, $p = 0{\cdot}70$) The average coronary prognostic index was 3·7 for patients admitted by the mobile unit and 4·0 for patients admitted by ordinary ambulance. Twelve month survival for those under 65 years was 66% for the mobile unit and 53% for the ordinary ambulances. Twelve patients were resuscitated outside hospital by the mobile unit and 10 (83%) of them were alive at 12 months. No successful resuscitations were carried out by ordinary ambulance.

Balloon dilatation of the aortic valve for critical aortic stenosis

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Balloon dilatation of the aortic valve (BAV) has been suggested as an alternative to aortic valve replacement in elderly or infirm patients with aortic stenosis (AS). We report our initial experience with this technique in patients who were considered to be unsuitable for operation because of severe left ventricular failure (3 patients) or coexisting disease (nine patients). Thirteen procedures were performed on 12 patients (mean age 65·5 yr (range 50–75). All had pure AS and were in New York Heart Association (NYHA) class III or IV. The mean transvalvar gradient was reduced from 81 mm Hg (range 40–140 mm Hg) to 48 mm Hg (range 20–80 mm Hg) ($p = 0{\cdot}008$). In one patient symptomatic restenosis required repeat dilatation. Fatal arterial thromboembolism occurred in two patients two days and seven days after BAV. Both had symptomatic peripheral vascular disease. Total procedure related mortality was three out of 13 procedures. All patients who survived BAV reported an improvement in symptoms of at least one NYHA class. Doppler assessment of the gradient after BAV correlated well with directly measured values. The high procedure related mortality may be attributed to the presence of severe coexisting medical disease or left ventricular failure in these patients.

We conclude that though BAV is an effective means of palliation for critical AS, it has serious risks for those most likely to benefit from it.

Syncope in athletes: the role of the Valsalva manoeuvre

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Syncope and near syncope have been reported in trained athletes. Although such episodes are often associated with bradyarrhythmias, some athletes, without detectable bradyarrhythmia complain of near syncope, particularly during high resistance training. We evaluated beat to beat changes in left ventricular volume associated with isometric exercise, dynamic exercise, and the standard and maximum Valsalva manoeuvres in five olympic athletes by means of a nuclear stethoscope. In one subject simultaneous intra-arterial blood pressure was also recorded. Changes were qualitatively similar in all subjects. Mean resting ejection fraction at rest was 66·6%. During isometric exercise (maximum handgrip for 10 seconds) the ejection fraction fell by an average of 4% when subjects breathed normally and by 18·6% with simultaneous Valsalva manoeuvre. During maximum Valsalva manoeuvre maintained for 10–15 seconds (simulating the manoeuvre performed during weight training) dramatic falls in the ejection fraction were seen such that in two mesomorphic subjects the left ventricular volume time-activity curve showed a flat response. Moreover, an arterial trace in one of these subjects showed a mean pressure of 50 mm Hg at the end of the procedure with a pulse pressure of 15 mm Hg. Background counts (representing blood in the pulmonary vascular bed) also decreased during maximum Valsalva.

We conclude that a dramatic fall in cardiac output occurs in trained athletes during the Valsalva manoeuvre, which may be partly responsible for near syncope observed in some athletes during heavy resistance training.

Clinical comparison of angiographically diagnosed primary and chronic thromboembolic pulmonary hypertension

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Classification of pulmonary vascular disease distinguishes primary (PPHT) and chronic thromboembolic (CTPHT) pulmonary hypertension, and it has been suggested that these two conditions have different angiographic appearances. We reviewed the clinical and investigative features of a large series of patients with these conditions in whom angiographic and haemodynamic data were available. Twenty one patients had arteriographic findings suggestive of PPHT (symmetrical peripheral vessel pruning) and 22 patients findings suggestive of CTPHT (asymmetrical vessel occlusion). Patients with PPHT were on average younger (mean 39 (range 9–62) years), and there were more female patients in this group (16 female, nine male). Patients with CTPHT (13 female, nine male) presented between the ages of 15 and 68 years (mean 46). Mean pulmonary artery pressure was significantly ($p < 0.01$) higher in the PPHT (67 mm Hg) than in the CTPHT (49 mm Hg) group. There were no other significant differences. All the patients were breathless; haemoptysis, chest pain, and symptoms interpreted as deep venous thrombosis were equally frequent. The mean duration of symptoms before diagnosis was not significantly different (PPHT 23 weeks, CTPHT 27 weeks). Physical signs, electrocardiographic changes, and abnormalities suggestive of pulmonary hypertension detected in chest radiographs were equally common. Thirty five patients died, but survival from the time of diagnosis was not significantly different in the two groups (PPHT (n = 19) mean 26 weeks (range 1–88); CTPHT (n = 16) mean 38 weeks (range 1–192)).

Histological differentiation between PPHT and CTPHT is impossible. Our data indicate that it is equally impossible to distinguish between the two conditions on the basis of clinical presentation or prognosis.

Early (24 hour) electrocardiographic stress testing in the evaluation of acute chest pain

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Altogether 231 patients with severe chest pain were admitted to this hospital during 1986. Within 24 hours 108 confirmed recent myocardial infarcts were identified; 38 patients were considered to exhibit unstable angina, and 76 patients had posed a diagnostic problem. Forty nine apparently stable patients proceeded to electrocardiographic stress testing (treadmill and Bruce protocol) within 24 hours after admission. Ten showed strongly positive results with significant atheroma on subsequent angiography. Five showed equivocal stress performance. All had normal or minimally diseased coronary vessels. There were no false positive results. Thirty four patients showed normal results on stressing (max heart rates 85%) at 24 hours and were discharged. All were reviewed after one year. No clinical events were recorded; three patients experienced variable chest pain, but all stress tests were again normal.

Thus early (24 hour) stress testing showed serious potentially threatening disease in patients with clinically mild unstable angina and also reliably identified many patients suitable for quick discharge.

In hospital delay in administration of thrombolytic treatment

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Administration of thrombolytic treatment to patients outside hospital in the early phase of acute myocardial infarction remains impractical or impossible in many health districts; but there may be scope for in hospital delays to be reduced. We analysed 50 consecutive patients entering the APSAC-Swift study who received thrombolytic treatment by simple intravenous bolus injection within 180 minutes from the onset of symptoms. Details of the study were well publicised in the recruiting hospitals. Electrocardiographic criteria for entry were ST segment elevation of 0·1 mV in two standard or 0·2 mV in two precordial leads. We found a delay in hospital of 25–150 minutes (median 77·5). This contrasted with a delay for opiate treatment (if given) of only 5–139 minutes (median 30) in the same patients. The delay out of hospital was 15–120 minutes (median 56), with a total delay of 60–180 minutes (median 150). The in hospital delay was less for those with strikingly abnormal electrocardiographic changes (ST elevation > 2 mV and reciprocal changes), those seen in the accident and emergency department by senior house officers on cardiology rotation, and those in whom life threatening arrhythmia occurred before thrombolytic treatment. In 14 patients treatment was delayed because of non-diagnostic changes in the initial electrocardiogram. A further 24 patients with diagnostic electrocardiographic changes were transferred to the coronary care unit before treatment because of lack of awareness about thrombolytic treatment, because of physicians' concern about reperfusion arrhythmias, or for administrative convenience (delay for patients treated in the accident and emergency department 25–75 minutes (median 35): delay for patients treated in the coronary care unit 65–150 minutes (median 105)).

There are significant in hospital delays in the administration of thrombolytic treatment that could be reduced by education, reassurance about reperfusion arrhythmias, and avoiding the tendency to wait until the end of any chosen time window. Less stringent electrocardiographic criteria (with a convincing history) would result in earlier treatment of some patients.

Do high risk patients with acute myocardial infarction benefit from early intravenous metoprolol?

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The ISIS I study and mega-analysis have shown that early intervention with beta blockade reduces mortality in acute myocardial infarction. The second largest study (MIAMI) was not sufficiently powerful to show reduced mortality. It may be that a high risk group can be selected in which the benefit of early intervention should be higher. Analysis of subgroups in the MIAMI study showed that metoprolol did confer a significant benefit to these patients. We tested this hypothesis in a randomly allocated double blind study of 800 patients admitted with suspected acute myocardial infarction who were given 15 mg metoprolol intravenously or equivalent placebo. None of the MIAMI risk factors, (age older than 60; previous myocardial infarction; angina pectoris; congestive heart failure; hypertension; diabetes; taking digoxin or diuretics, or both; and abnormal electrocardiogram) individually identified a group in which metoprolol was associated with a significant reduction in mortality at three months. The relative prognostic importance of these factors correlated poorly with the MIAMI study (Spearman's correlation test). Three or more risk factors were simultaneously present in 38% of our patients, and mortality in those given metoprolol was 9·6% compared with 13·8% in those given placebo.

Our data are consistent with the finding in the MIAMI study that patients at high risk show a reduction in mortality of about 30% when given intravenous metoprolol. In a study of 800 patients this difference was not significant. In clinical practice the reduction is unlikely to be apparent in a coronary care unit with an average throughput.

Doppler flow patterns reflect the pulmonary artery pressure in ductus arteriosus

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The Doppler spectral pattern of flow through the ductus arteriosus was studied in 33 patients in whom aortic and pulmonary artery pressure were measured at catheterisation (in 18 simultaneously with two catheters). Flow was continuous throughout the cardiac cycle and exhibited four distinct wave forms: (*a*) high maximum velocity occurring in late systole with gradual fall throughout diastole; (*b*) high systolic velocity with rapid fall to a very low value in early diastole and maintained throughout; (*c*) low velocity throughout with maximum in late diastole; and (*d*) bidirectional flow. The appearance of (*a*) was associated with normal or minimally raised pulmonary artery pressure (systolic below 50 mm Hg, diastolic below 30 mm Hg), that of (*b*) with raised pulmonary artery pressure (systolic above 50 mm Hg, diastolic above 30 mm Hg, and that of (*c*) and (*d*) with pulmonary artery pressure at systemic values. Comparison of the Doppler and catheter measured pressure differences between the great arteries showed a poor correlation for both the peak and trough readings.

The signals were more readily identified with colour Doppler flow mapping but could also be recorded with a stand alone transducer. Doppler ultrasound clearly shows ductal flow; the flow wave form gives an indication of the pulmonary artery pressure, but measurement of pressure by application of the Barnoulli equation to the flow velocities is not reliable.

Arginine vasopressin abolishes the diuretic effect of atrial natriuretic factor in man

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Chronic heart failure is characterised by abnormal concentrations of hormones including inappropriately high arginine vasopressin (AVP) concentrations. Patients with this condition also have raised atrial natriuretic factor (ANF) concentrations, yet chronic heart failure is typified by sodium and water retention. Exogenous ANF also fails to stimulate a diuresis in patients with chronic heart failure. To investigate whether AVP might be blocking the effect of ANF in chronic heart failure, AVP alone, ANF alone, and AVP and ANF together were infused into nine normal subjects during steady state maximal water diuresis. A dual placebo (P) infusion day was also performed. The dose of AVP (0·003 pmol/kg/min) and ANF (15 pmol/kg/min) were chosen so as to mimic the circulating concentrations of these hormones found in chronic heart value. The change in urinary flow rate (ml/min (SEM)) from baseline was: (*a*) P + P −0·5 (0·29), −0·46 (0·35); (*b*) AVP + P −6·22 (0·92)*, −6·78 (0·9)*; (*c*) P + ANF +1·68 (0 35)*, +0·98 (0·42); (*d*) AVP + ANF −4·57 (0 96)*, −5·71 (0·97)*. The change in urinary sodium excretion (μmol/min (SEM)) was: (*a*) P + P −11·8 (3·9), −9·0 (5 3); (*b*) AVP + P −9·4 (2·6), −2·5 (8·9); (*c*) P + ANF +29·7 (7·1)*, +23 4 (6·9)*; (*d*) AVP + ANF +38·5 (11·4)*, +26 0 (11·5)* (*$p < 0{\cdot}01$ *v* baseline).

These results show that AVP abolishes the diuretic but not the natriuretic effect of ANF in man. This suggests that other neuroendocrine influences may be required to blunt the natriuretic effect of ANF in chronic heart failure or that haemodynamic factors may be more important in the control of sodium excretion.

Characteristics of energy delivery during catheter discharges in man: primary role of voltage in successful ablation

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The precise mode of action of catheter ablation is unknown, but barotrauma, current, voltage, and heat have all been implicated. We examined recordings of voltage, current, derived energy, and impedance from 39 shocks with the National Heart Hospital (NHH) ablater (capacitive discharge) in 14 patients and compared them with results with a conventional power source and shocks in saline. Changes in impedance were similar in vivo and in vitro and of four types. (1) A short (< 50 μs) transient high impedance due to initial polarisation. (2) A subsequent constant impedance for non-arcing shocks, but a fall in impedance for arcing shocks after a mean 0·33 (SEM 0·02) ms, proportional to delivered energy ($r = 0{\cdot}78$, $p < 0{\cdot}001$); in vitro recordings showed that the fall in impedance coincided with the onset of arcing. (3) A steep rise in impedance after arc extinction. Complete insulation occurred in vitro but not in vivo as the electrode tip remains in partial contact with myocardial tissue. (4) A return to a baseline impedance value similar to that for non-arcing shocks. With the NHH ablater successful ablation of atrioventricular conduction was performed with energy, peak current, and peak voltage of 19 7 (11·2) J, 18·8 (8·6) A, and 2328 (919 V, respectively; successful ablation with a conventional defibrillator was achieved with 221·4 (77·3) J, 44·9 (14·9) A, and 2093 (600) V. Lower energy and pressure changes with NHH shocks suggest heat and barotrauma are not important for success. Survival curve analysis of atrioventricular conduction showed that energy and peak current were dissimilar for the two power sources but that the voltages were not significantly different, suggesting the primary importance of voltage in termining outcome.

Thus voltage is the likely mediator of useful cardiac damage during catheter ablation in man. This result has implications for future designs of power source.

Increased rate of first myocardial infarction in immigrant Asians

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Mortality and morbidity from coronary disease in Asians living in Britain is thought to be higher than in whites, but estimating infarction rates from hospital activity analysis records can be unreliable. We prospectively studied 78 consecutive patients presenting with myocardial infarction. All patients were men aged less than 60 and resident in the London Borough of Harrow at the time of the 1981 census. To ascertain the possible existence of ethnic bias with respect to general practitioners' referrals in patients with suspected myocardial infarction a questionnaire survey of 99 local general practitioners was performed. No such bias was found. Asians were younger at presentation (47·6 *v* 54·7 years) (p < 0·001). Twenty nine myocardial infarctions occurred in a population of 5188 Asian men versus 49 in 31 308 whites (p < 0·000005). Twenty one Asians were smokers versus 38 whites. Five Asians were known diabetics versus one out of 49 whites. Predischarge glucose tolerance tests showed a further seven patients with diabetes or impaired glucose tolerance in the Asian group (total 12 out of 29) and nine in the white group (total 10 out of 49) (p < 0·01). Twelve Asians had a positive family history versus 21 out of 49 whites (NS).

We conclude that male Asians in Harrow have a much higher rate of myocardial infarction than whites. The first infarction occurred at a younger age in Asians, and the prevalence of diabetes is much higher in Asians with infarction than in whites. Smoking habits and family history were not different between the groups.

Effects of β adrenergic and calcium channel blocking agents on the circadian distribution of silent myocardial ischaemia

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One hundred and fifty patients (mean age 55 years) underwent 6264 hours of ambulatory ST monitoring when no longer taking routine anti-anginal therapy. Altogether 598 episodes of significant ST change (≥1 mm) were recorded (447 silent); 77% of silent ischaemic episodes occurred during the waking hours (0730–2230). Two subgroups were studied among these patients. Thirty three patients also had ST monitoring (1313 hours) while taking nifedipine and 41 patients (1581 hours) while taking atenolol (A). In the subgroup who had stopped taking nifedipine 43·8% of 129 silent episodes occurred between 0730 and 1330 (AM) and 31·5% of episodes between 1330 and 1930 (PM) (ratio = 1·39). In the patients taking nifedipine 40·1% of 136 silent episodes occurred AM, and 27·7% PM (ratio = 1·45). In the subgroup who had stopped taking atenolol 34·5% of 237 silent episodes occurred AM and 30·3% PM (ratio = 1·14). In patients taking atenolol 23·0% of 135 silent episodes occurred AM and 36·3% PM (ratio = 0·63). The frequency of silent myocardial ischaemia (SMI) in the six hour AM period was significantly higher than the average of the other three six hour periods in both subgroups who were no longer being treated and in the patients receiving nifedipine (p < 0·01). In contrast, in the patients taking atenol SMI increased significantly compared with the average of the other three periods.

In summary, atenolol led to a reversal of the distribution of silent ischaemic episodes from the morning to the evening hours. In contrast, nifedipine did not significantly alter the circadian distribution of silent ischaemic episodes. This is of therapeutic importance as the incidence of both myocardial infarction and sudden death is greatest in the morning hours and the circadian rhythm of acute myocardial infarction is reported to be altered by β adrenergic blocking agents.

Initial electrocardiograms and outcome for patients seen by a mobile coronary care unit within four hours of the onset of suspected myocardial infarction

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With the advent of thrombolytic therapy for patients with suspected myocardial infarction analysis of the initial electrocardiogram (ECG) is crucial in decision making. Thus we analysed the initial ECGs of 89 consecutive patients with suspected myocardial infarction who were seen within 4 hours after the onset of chest pain by a mobile coronary care unit (MCCU) and survived to be admitted to hospital. We studied 67 men and 22 women whose mean age was 61 (25–81). MCCU response time ranged from 5–45 minutes (mean 13·0), and mean time from onset of pain to arrival of the MCCU was 84 minutes (range 15–240). The initial ECG was considered positive if there was evidence of infarction (pathological Q waves or ST segment elevation), ischaemia (ST segment depression or T wave inversion, or both), or left bundle branch block. A diagnosis of myocardial infarction was confirmed in 40 of 89 (45%) patients, 25 (28%) patients had acute ischaemia, and 24 (27%) other diagnoses. Of the 35 patients seen within the first hour, five (14%) with a normal initial ECG had a proved myocardial infarction. Two of the 34 (6%) patients seen in the second hour had a proved myocardial infarction, one of the 10 (10%) seen in the third hour, and none of those with a normal initial ECG seen in the fourth hour. Analysis of the normal initial ECGs showed that in the first hour five out of 11 (45%) patients had a proved myocardial infarction, in the second hour two out of 12 (17%), in the third hour 1 out of five (20%), and in the fourth hour none out of four. Of those with an initial positive ECG for myocardial ischaemia but no proved myocardial infarction there were 12 out of 35 (34%) in the first hour, six out of 34 (18%) in the second hour, four out of 10 (40%) in the third hour, and three out of 10 (30%) in the fourth hour.

We conclude that 9% (eight out of 89) of patients presenting within four hours after the onset of chest pain had a myocardial infarction but normal initial ECG. The highest percentage of normal initial ECGs associated with an acute myocardial infarction were recorded within the first hour after the onset of symptoms.

Restrictive cardiomyopathy and constrictive pericarditis: non-invasive distinction by digitised M mode echocardiography

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Restrictive cardiomyopathy and constrictive pericarditis may be difficult to distinguish on clinical grounds or simple investigation; cardiac catheterisation has been the gold standard for diagnosis but does not always allow distinction. Using a Summagraphics digitiser and Prime 750 computer system we have digitised the M mode echocardiograms of patients with restrictive cardiomyopathy and constrictive pericarditis (n = 10) and those of normal subjects matched for age and sex (n = 20). In restrictive cardiomyopathy restrictive pathophysiology was shown by reduction in the following when compared with controls: (*a*) fractional shortening 22% (9·8) *v* 36% (3·6), p < 0·001; (*b*) peak left ventricular filling rate 7·5 (3·3) *v* 12 (12·6) cm/s, p < 0·001; (*c*) left ventricular peak emptying rate −5·3 (1·7) *v* −8·3 (1·1) cm/s, p < 0·001; (*d*) percentage posterior wall thickening 24% (12) *v* 35% (7), p < 0·007; (*e*) peak left ventricular posterior wall thickening rate −4·1 (2·5) *v* −5·8 (1·8) cm/s, p < 0·02; and (*f*) peak left ventricular posterior wall thinning rate 2·6 (0·9) *v* 3·4 (0·7) cm/s, p < 0·008. When patients with constrictive pericarditis were compared with controls the only significantly different variables were a decreased peak left ventricular filling rate (8·8 (2·5) cm/s, p < 0·004) and an increased peak left ventricular posterior wall thinning rate (6 (2·8) cm/s, p < 0·01). In patients with constrictive pericarditis, however, peak left ventricular emptying rate (−8·5 (2·8) cm/s, p < 0·006), percentage posterior wall thickening (47% (−15), p < 0·008), peak left ventricular posterior wall thickening rate (−6·7 (1·9) cm/s, p < 0·007), and peak left ventricular posterior wall thinning rate (6 (2·8) cm/s, p < 0·004) were all significantly increased compared with in patients with restrictive cardiomyopathy.

We conclude that digitisation of M mode echocardiograms, with particular attention to posterior wall function, may be a useful adjunct to cardiac catheterisation in restrictive cardiomyopathy and constrictive pericarditis.

Quantitative echocardiographic tissue characterisation after cardiac transplantation

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Detection of myocardial changes after cardiac transplantation usually requires myocardial biopsy. To assess a possible role for echocardiography single end diastolic frames recorded with 6 bit grey levels with standardised gain and depth compensation settings were stored and analysed off line. Myocardial areas of interest were located in the septum and posterior wall, and mean backscattered amplitude automatically determined in samples of 100–200 pixels after speckle reduction. Results in 40 patients up to seven years after transplantation were compared with results in normal subjects matched for age and expressed in 0·9 dB units above zero. Mean backscattered amplitude was increased after transplantation to 13·6 (3·2) u (normal 6·6 (1·9); p < 0·001) with minimal overlap in individual patients. Mean backscattered amplitude within the first year after transplantation (12·9 (2·7) u) was less than that after one year (14·3 (3·7) u; $p < 0{\cdot}03$). Mean values of backscattered amplitude greater than 15 u occurred in 18 patients in the septum or posterior wall. In eight patients this correlated with evidence on biopsy grade 1 rejection and in two patients with fibrosis. Greater degrees of rejection were not seen in any patient. In the remaining patients, high values of backscattered amplitude were seen in all at five at risk beyond four years, but only three of 26 before that ($p < 0{\cdot}001$).

Thus myocardial backscattered amplitude is greater than normal after transplantation and increases with time. These increases reflect, in part, fibrosis or low grade rejection. This method may be useful in detecting, and in particular in determining, the myocardial distribution of these processes.

Diurnal variation of pulmonary artery pressure in chronic heart failure

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Variation in pulmonary artery pressure in patients with chronic heart failure may reflect changes in posture, pulmonary artery tone, and left ventricular function. To investigate the nature of diurnal variation in pulmonary artery pressure in chronic heart failure eight men aged 50–72 years who were free of angina and with treated chronic heart failure caused by ischaemic heart disease underwent continuous ambulatory pulmonary artery pressure recording with a transducer tipped catheter. A frequency modulated signal was recorded over 24 to 48 hours and played back on a paper chart recorder. The systolic and diastolic pressure was measured every 12 minutes by averaging pressures over one minute intervals. The mean daytime systolic pulmonary artery pressure was 29·6 (SD 5·0) mm Hg and diastolic pressure 13·7 (5·6) mm Hg. During the night the systolic pressure rose to 36·0 (4·1) mm Hg ($p < 0{\cdot}005$) and the diastolic to 17·6 (2·9) mm Hg ($p < 0{\cdot}001$). The mean change in systolic pressure from day to night was 5·1 (3·2) mm Hg and from standing to lying 9·3 (2·3) mm Hg ($p < 0{\cdot}025$). The mean change in diastolic pressure from day to night was 3·8 (1·7) mm Hg and from standing to lying 6·4 (2·1) mm Hg ($p < 0{\cdot}025$). In six of the eight patients there was considerable diurnal variation in pulmonary artery pressure. In four of them recordings were obtained over 48 hours, and the diurnal variation in the first 24 hours was similar to that in the second 24 hours. In two of the eight patients there was no pressure rise during the night. Although the diurnal variation in pressure might be partly explained by postural change, no correlation was found in the whole group of patients between postural pressure changes and diurnal variation.

Thus in patients with chronic heart failure diurnal variation in systolic and diastolic pulmonary artery pressure is common and may have important implications for the selecting and timing of treatment.

Diagnostic value of comparison of ventriculoatrial intervals during junctional tachycardia and right ventricular apical pacing

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We postulated that comparison of ventriculoatrial intervals during junctional tachycardia and continuous right ventricular apical pacing may provide similar diagnostic information to that obtained from the insertion of right ventricular apical extrasystoles during tachycardia. Patients with either atrioventricular re-entrant tachycardia (AVRT) ($n = 23$) by a single atrioventricular pathway or atrioventricular nodal re-entrant tachycardia (AVNRT) ($n = 16$) were studied. Ventriculoatrial intervals were measured during tachycardia, the ventricular pacing being at the same rate as the tachycardia and following a ventricular extrasystole delivered at the minimum reset interval (minimum prematurity of a ventricular extrasystole that advanced the subsequent atrial complex > 10 ms). The difference between the minimum ventriculoatrial interval during tachycardia and ventricular pacing was closely related to both the minimum reset interval ($r = 0{\cdot}92$, $p < 0{\cdot}001$) and the difference between the minimum ventriculoatrial interval during tachycardia and following a ventricular extrasystole delivered at the minimum reset interval ($r = 0{\cdot}97$, $p < 0{\cdot}001$) in the 23 patients in whom the minimum reset interval could be determined. The ratio between the minimum ventriculoatrial interval during tachycardia and ventricular pacing could be determined in all the patients and was 1·53–1·68 in atrioventricular re-entrant tachycardia with right free wall (two patients), 0·94–1·29 in that with anteroseptal defect (three patients), 0·91–1·08 with posteroseptal defect (five patients), and 0·48–0·71 with left free wall pathways (13 patients) while it was −0·32–0·27 in atrioventricular nodal re-entrant tachycardia (16 patients). The ratio was more descriminative when corrected for ventricular latency and was also useful when calculated from the high right atrial electrogram.

We conclude that comparison of ventriculoatrial intervals during tachycardia and right ventricular apical pacing can descriminate between the mechanism of tachycardia and the site of pathway if present. It provides similar information to that obtained from right ventricular apical extrasystoles during tachycardia with the advantage that it can be determined in all cases.

Technetium-99m-2-methyl isobutyl isonitrile (MIBI): a new imaging agent for localisation of myocardial infarction

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A new myocardial imaging agent (technetium-99m-2-methyl isobutyl isonitrile (MIBI)) was evaluated in locating reduced perfusion in eight patients with recent myocardial infarction that was confirmed by cardiac enzyme activities and serial electrocardiograms. MIBI has advantages over thallium-201, with a higher energy and a slow myocardial clearance of five hours. Resting first pass radionuclide ventriculography was performed with a bolus injection of MIBI followed within two hours by perfusion imaging in three standard projections after a single MIBI injection. Images were reported by two independent observers. One patient had a previous anterior Q wave infarction with no anterior perfusion abnormality and normal wall motion. Seven patients had new Q wave infarctions and one had septal ST segment depression. All patients had regions of abnormal perfusion that corresponded with regional wall motion and the site of electrocardiographic changes. One patient with an anterior myocardial infarction and reduction of R wave amplitude showed anterior and posteroinferior perfusion abnormalities but only apical akinesis. A further patient had posterior hypoperfusion with an inferior myocardial infarction on electrocardiography and first pass radionuclide ventriculography. The extent of hypoperfusion, wall motion abnormalities, and ejection fraction were closely related in all patients.

This agent can be used not only for detecting abnormal myocardial perfusion but also for identifying regional wall motion abnormalities by first pass radionuclide ventriculography in patients with myocardial infarction.

Evidence of subclinical myocardial necrosis in patients with unstable angina detected by indium-III antimyosin antibody imaging

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In a prospective study of 103 patients admitted to hospital for investigation of suspected acute myocardial infarction (AMI) or unstable angina antimyosin antibody (FAB) (In-AM) imaging was performed to evaluate this new scintigraphic technique. Within 48 hours after experiencing chest pain all patients received 0 5 mg In-AM labelled to 74–83 MBq with indium-III. Gamma camera imaging was performed at 24 and 48 hours. Serial cardiac enzyme activities of creative kinase and creatine kinase MB were measured and 12 lead electrocardiograms (ECG) were obtained daily and during chest pain. Of 98 patients imaged, 64 had AMI (45 had Q and 19 non-Q wave AMI), and 34 showed no evidence of AMI (unstable angina in 13 and no AMI or resting ischaemia in 22). The overall sensitivity and specificity for detecting AMI were 98% and 91%, respectively. Three out of the four "false positive" scans were noted in three patients with unstable angina. All three patients had severe three vessel coronary artery disease, and the uptake of In-Am was confined to the myocardial segments supplied by a critically narrowed artery; one patient died suddenly while awaiting operation one week after imaging.

Our results confirm those of experimental work showing a high degree of specificity of In-AM to bind with the acutely necrotic myocardium. Thus the myocardial uptake of In-AM in the patients with unstable angina may represent subclinical myocardial necrosis in the absence of the typical rise in cardiac enzyme activities and changes in electrocardiograms.

Grading programmed electrical stimulation for ventricular tachycardia

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Programmed electrical stimulation (PES) for ventricular tachycardia (VT) is usually performed in a specific order of increasing numbers of extrastimuli (ES) and increasing drive rates. Because PES is stopped when VT is induced it is not known whether this represents increasing aggression or is a random order. All eight stages of our PES, with one then two ES from the right ventricular apex in sinus rhythm and three drive rates (100, 120, and 140 beats/min), were performed sequentially regardless of whether VT was induced at any stage. The protocol was stopped if the patient was distressed by the VT or it was difficult to stop with PES. If only non-sustained VT was induced, 3 ES were then added in sinus rhythm and in the three drive rates. Twenty one patients (mean age 57 years (range 27–75)) completed the protocol. Sixteen had ischaemic heart disease and five had morphologically normal hearts. VT was induced in all of them: it was sustained (>30 s) in 13, non-sustained (⩾5 beats, <30 s) in seven, and both types occurred in one patient at different stages. In all 21 patients VT was induced by a 140 beats/min drive rate. In 17 it was induced by a drive rate of 120 beats/min, in 16 it was induced by 100 beats/ min, and in six it was induced in sinus rhythm. Two patients had VT induced only by 1 ES, eight patients only by 2 ES, and three patients only by 3 ES. Five patients had VT induced by both 1 and 2 ES, two patients by both 2 and 3 ES, and one patient by 1, 2, and 3 ES. In only three patients was VT not induced at an intermediate drive rate with the same number of ES if the higher and lower rate induced VT. The cycle length of the VT induced at a later stage (366 (95) ms) was not significantly faster than that induced at an earlier stage of the protocol (387 (98) ms).

It seems that a protocol of sinus rhythm followed by increasing drive rates represents a stepwise increase, separately for 1, 2, and 3 ES, in the likelihood of inducing VT. In this study a drive rate of 140 beats/min with 1, 2, or 3 ES was as effective as the entire PES in inducing VT.

Platelet activation in unstable angina

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We investigated the importance of platelet activation in unstable angina pectoris by examing the temporal relation between the occurrence of episodic platelet activation and spontaneous myocardial ischaemia. Continuous electrocardiographic ST segment recording was performed for 24–96 hours in 11 patients with unstable angina treated with intravenous isosorbide dinitrate and oral diltiazem but no cyclo-oxygenase inhibitors. Platelet activation was assessed by radioimmunoassay of the main thromboxane metabolite, 11-dehydro-thromboxane B2 (TXB2), from serial eight hours urine collections. A total of 38 episodes of ischaemia were recorded (23 asymptomatic) and 56 urinary samples collected. The mean peak TXB2 value in each patient was 3389 (SD 2745) pg/mg creatinine (range 697–10 897), which was significantly greater ($p < 0·01$) than in 23 control patients without unstable angina or myocardial ischaemia (356 (151) (range 80–633)) or 20 patients with peripheral vascular disease (426 (160), (range 160–899), $p < 0·01$). In 46% of all urine samples TXB2 excretion was increased, but only 12% were associated with ST segment changes. TXB2 was raised in association with half of all episodes of myocardial ischaemia, during 78% of all episodes of chest pain, but also in 37% of urinary collections not associated with ST segment changes of pain.

Although episodes of intense platelet activation may often be observed in unstable angina, the relation between TXB2 excretion and the occurrence of myocardial ischaemia is highly variable; ischaemic episodes are frequently not associated with platelet activation and vice versa. Platelet activation is important but may be only one mechanism involved in the pathogenesis of unstable angina.

How important is pain during exercise induced myocardial ischaemia?

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Angina pectoris remains the main indication for coronary artery surgery, though most episodes of myocardial ischaemia are asymptomatic. We assessed whether the presence or absence of angina pectoris during formal exercise testing was related to the anatomical extent of disease or functional impairment during exercise. Left ventricular ejection fraction (LVEF) was measured every two minutes during symptom limited bicycle exercise in 34 patients with documented coronary artery disease, who were studied when they were not taking antianginal treatment. Eight, 16, and 10 patients had one vessel, two vessel, and three vessel disease, respectively, and the coronary scores for the percentage of myocardium supplied by stenosed vessels were 30 (4)%, 52 (3)%, and 73 (7)%, respectively.

During exercise the limiting symptom was angina ($n = 19$) or breathlessness ($n = 15$). The presence of angina was not associated with a lower exercise time (421 (31) *v* 455 (64) s), ST depression (1·4 (0·3) *v* 1·1 (0·30) mm), exercise LVEF (47 (3) *v* 49 (3))% or fall in LVEF (−13 (2) *v* −12 (2)). Mean vessel disease and coronary score were similar (2·1 (0·1) *v* 2·1 (0·2) and 53 (4)% *v* 53 (5)%, respectively). ST depression (> 1 mm) developed in 22 patients. Exercise time was similar (angina *v* no angina) (452 (45) *v* 406 (42) s) as was the proportion developing angina (17 out of 22 *v* seven out of 12). ST depression was associated with a lower exercise LVEF (44 (2) *v* 56 (3) $p < 0\cdot005$), greater fall in LVEF (−15 (2) *v* −8 (3) $p < 0\cdot02$), and more severe vessel disease (2·3 (0·1) *v* 1·6 (0·2); $p < 0\cdot005$) and coronary score (62 (3)% *v* 37 (3)%; $p < 0\cdot001$). The degree of ST depression correlated with the fall in LVEF ($r = -0\cdot5$; $p < 0\cdot002$) and coronary score ($r = 0\cdot6$, $p < 0\cdot001$).

Thus the symptom of angina pectoris during formal exercise testing bore no relation to the severity of disease and should not be a major criterion on which to base a management strategy. ST segment depression was a more reliable marker of disease and functional impairment during exercise.

Infarct size can be measured acutely in developing myocardial infarction

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In patients with acute coronary artery occlusion flow markers can reliably detect the site of infarction. Gate perfusion imaging with thallium-201 was used to estimate infarct size when the patient was admitted to coronary care. Altogether 120 consecutive patients were imaged at a mean time of 86 minutes from arrival at hospital by a mobile gamma camera after an intravenous injection of 60 MBq of thallous chloride. Infarct size was estimated in the 82 patients who subsequently proved to have myocardial infarction and the size was correlated with clinical (Norris index) and enzymatic (peak creatine kinase and creatine kinase MB release curves) estimates. In patients with first infarction perfusion and enzymatic estimates of infarct size were significantly correlated: $r = 0\cdot7$ ($p < 0\cdot001$) for 22 patients with anterior infarction and $r = 0\cdot5$ ($p < 0\cdot001$) in 32 with inferior infarction. In these groups there was no correlation between either the perfusion of enzymatic measure of infarct size and Norris index or ejection fraction. In contrast, in 24 patients who died there was a significant correlation between clinical findings (Norris index) and total perfusion defect ($r = 0\cdot6$; $p < 0\cdot001$) and ejection fraction and total perfusion defect ($r = 0\cdot5$; $p < 0\cdot009$), but not with enzymatic measures of infarct size or any other variable. Eleven patients died within 14 days and the correlation between Norris index and total perfusion defect was 0·8 ($p < 0\cdot001$).

Gated perfusion imaging on admission reflects the volume of myocardium affected and thus infarct size and should be of value in predicting the clinical outcome in patients with acute myocardial infarction.

Sublingual nifedipine and coronary flow

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Sublingual nifedipine is frequently used by patients for the relief of angina. To investigate the mode of action 12 patients were studied at the time of routine angiography. Heart rate was obtained from the electrocardiogram and blood pressure by femoral arterial line. Regional myocardial nutrient blood flow was assessed from the clearance of xenon-133 after direct intracoronary injection. Imaging was performed in the 40° left anterior oblique projection with a mobile gamma camera. Measurements of both coronary arteries were made at rest and 3–7 minutes after 10 mg sublingual nifedipine. There was no significant change in heart rate or mean arterial pressure (98 (3) to 96 (4) mm Hg). In 12 distributions supplied by vessels that were not significantly diseased flow increased significantly by 16%, from a mean of 63·1 (6·3) to 74·7 (8·1) ml/100 g/min ($p < 0\cdot02$). In 24 regions supplied by coronary vessels that were significantly diseased mean flow increased from 57·9 (4·1) to 60·8 (5·9) ml/100 g/min, representing an overall 5% increase in flow. This is in contradistinction to the effects of sublingual nitrate, with which flow fell by 14% ($p < 0\cdot01$) in distributions supplied by coronary arteries with high grade obstructions. In regions supplied by collaterals, after nifedipine, flow increased from a mean of 38·3 (4·7) to 72·6 (8·9) ml/100 g/min, whereas with sublingual nitrate collateral flow is reduced. These results show that nifedipine taken sublingually acts as a coronary vasodilator, and this may be the mechanism for relief of angina in patients with obstructive coronary disease.

Prospective study of atrioventricular conduction in patients with sinoatrial disease

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Many patients with sinoatrial disease could be effectively treated with atrial demand (AAI) pacing but for the development of atrioventricular block in a few. If this small group could be identified before pacemaker implantation it would prevent unnecessary insertion of two leads. A prospective study of 152 patients paced for sinoatrial disease in the past eight years was undertaken. Sixty (40%) patients were paced in ventricular demand (VVI) mode. The remainder underwent electrophysiological study at the time of pacemaker implantation. If atrioventricular conduction was normal, the patient was paced AAI. If abnormal, both ventricular and atrial leads were implanted and the patients sequentially paced (DVI). Results: 52 patients (34%) were paced in AAI mode. Mean age at implantation was 66·6 years and mean follow up time 29·4 months. No patients developed conduction disease requiring change of pacing mode. Five patients (9·6%) died. Thirty four patients (22%) were paced DVI. The average age at implantation was 66·0 years. Mean follow up was 24·7 months. Two patients (3·9%) died. Average age of patients paced VVI was 72·1 years and mortality was 12 (20%). A remaining six patients were paced in other modes.

Electrophysiological studies at pacemaker implantation in patients with sinoatrial disease can identify a patient group who did not develop atrioventricular disturbance during follow up. Such patients can be safely and economically paced in AAI mode.

Relative contributions of myocardial elastic modulus and cavity geometry in determining left ventricular cavity stiffness in man

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To investigate the relative contributions of geometrical factors and myocardial elastic modulus (E) to overall left ventricular cavity stiffness simultaneous biplane angiograms and micromanometer pressures were recorded in 10 patients with left ventricular disease, and digitised frame by frame. Left ventricular volumes (V) were determined by three dimensional reconstruction. Regional left ventricular wall stresses were estimated by finite element analysis with a 72 brick model, which allowed for normal variation in fibre orientation across the wall. Values of E were determined by matching the volumetric change with incremental pressure on a frame by frame basis, throughout diastasis, from the end of rapid filling until the onset of atrial systole. Left ventricular cavity compliance, expressed as $\Delta V/\Delta P$, varied widely, from 0·23 to 189 cm^3 mm Hg. In all patients there was a linear relation between E and 1/(cavity stiffness) throughout diastasis ($r > 0{\cdot}95$ for all patients). Dimensional analysis indicated its slope to be a function of cavity volume, relative wall thickness, and cavity shape: $V(dP/dV).\ 1/E = k(t^{0{\cdot}8}/r).(L^{1{\cdot}2}/r)$, where r = minor axis, L = long axis, t = wall thickness, and k is a constant. Retrospective calculation of cavity stiffness from these data gave $r = 0{\cdot}995$.

Thus measured left ventricular cavity stiffness in man depends only in part on myocardial elastic modulus; it is modified to a large extent by the geometrical properties of the ventricle and, in particular, by cavity shape.

Can Doppler assessment of left ventricular function distinguish hypertrophic cardiomyopathy from other causes of diastolic dysfunction?

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Analysis of left ventricular filling by pulsed Doppler reflects the diastolic function of the heart. The specificity of this analysis, however, has not been readily ascertained. To evaluate the incidence of diastolic abnormalities we investigated 15 patients with aortic stenosis, 52 patients with myocardial infarction, 20 patients with hypertrophic cardiomyopathy, and 33 normal subjects. From the diastolic flow velocity profile, peak velocity (cm/s) during the early filling (E wave), the atrial contraction (A wave), and the ratio of A to E wave were measured. Twenty nine of of 52 (56%) patients with myocardial infarction, nine out of 15 (60%) with aortic stenosis, and 14 out of 20 (70%) with hypertrophic cardiomyopathy had at least one of the above diastolic indexes outside the 95% confidence limits of the control group. The E wave was lower in patients with hypertrophic cardiomyopathy than in normals (53 (15) *v* 61 (11), $p < 0{\cdot}025$), but was similar to the normal subjects in patients with myocardial infarction and aortic stenosis. The A wave was elevated in all three groups of patients when compared with the normal subjects (39 (10); 56 (11) in hypertrophic cardiomyopathy ($p < 0{\cdot}01$); 51 (19) in myocardial infarction ($p < 0{\cdot}001$); and 67 (25) in aortic stenosis ($p < 0{\cdot}005$)). The A to E wave ratio was also raised in hypertrophic cardiomyopathy (1 1 (0·52); $p < 0{\cdot}005$) in myocardial infarction (0·98 (0·52); ($p < 0{\cdot}001$), and in aortic stenosis (1 1 (0·48); $p < 0{\cdot}005$) when compared with the normal subjects (0·69 (21)). The A wave was higher than the E wave in 20 out of 52 (38%) patients with myocardial infarction, in seven out of 15 (47%) patients with aortic stenosis, and in 11 out of 20 (55%) patients with hypertrophic cardiomyopathy, but in only two out of 33 (6%) normal subjects.

Pulsed Doppler shows abnormalities of filling in a high proportion of patients with hypertrophic cardiomyopathy, aortic stenosis, and myocardial infarction. The main characteristic of the Doppler inflow pattern in these patients is the significantly increased velocity during the atrial contraction. Such abnormalities of left ventricular filling are more common in patients with hypertrophic cardiomyopathy than in those with aortic stenosis or myocardial infarction but not specific for any of the three diseases.

Postoperative cardiac complications in elderly patients with fractured femoral neck

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The frequency and principal determinants of cardiac complications (myocardial infarction (MI), congestive heart failure (CHF), and cardiac death (CD)), were investigated in 199 consecutive elderly patients with femoral neck fractures who were randomly assigned to receive either general or spinal anaesthesia for surgical fixation. Postoperative cardiac complications were diagnosed clinically by comparison of preoperative and postoperative electrocardiograms and chest *x* rays, and by estimating serum concentrations of creatine kinase MB (CK-MB). Blood samples were taken immediately before operation and for five days after operation. MI was defined by CK-MB concentrations of >35 U/l and reinfarction as $>120\%$ of a raised preoperative value. Cardiovascular and noncardiovascular data in the general anaesthesia and spinal anaesthesia groups were similar before operation. Seven per cent of patients had MI before operation; this was associated, but not significantly, with a 21% reinfarction rate. The distributions of postoperative CHF and CD (5·5% and 4 5%) were not significantly different in the group given general anaesthesia. Postoperative MI rates, 14% in general anaesthesia and 5% in spinal anaesthesia, differed significantly ($p < 0{\cdot}05$) and general anaesthesia was the only significant determinant of postoperative MI. MI was not associated with chest pain or electrocardiographic change and 90% had occurred by the third post operative day. Postoperative CHF was associated significantly with history or presence of preoperative CHF ($p < 0{\cdot}001$), preoperative MI ($p < 0{\cdot}001$), and with age $\geqslant 80$ ($p < 0{\cdot}05$). CD was significantly associated with preoperative CHF ($p < 0{\cdot}01$) and with perioperative MI ($p < 0{\cdot}05$).

Clinical significance of painless ST segment depression on exercise after myocardial infarction

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In order to investigate the clinical significance of painless ST segment depression on exercise, 105 patients were studied prospectively six weeks after myocardial infarction. Patients underwent stress testing by a modified Balke's protocol and left ventricular ejection was measured within three days of the stress test. Thirty one patients were symptom free with no ST change (group 1), 28 stopped with angina and/or dyspnoea with significant ST depression (group 2), 25 were symptom free but had significant (>1 mm) ST depression (group 3), and 21 had symptoms with no ST change (group 4). The total mean (SD) exercise time in group 3 (9·1 (3 6) min) was not significantly different from that in group 1 (10 (4 4) min) or group 2 (7·9 (3·3) min), but it was significantly different from that in group 4 (6 (4·1) min) ($p < 0{\cdot}01$). Resting ejection fraction was 53 (11·8%) in group 3 but was not different from group 1, 49 (11·6)% ($p =$ NS), but was significantly higher than in group 2 (45 (13·3)% ($p < 0{\cdot}05$)) and group 4 (41·6 (17·2)% ($p < 0{\cdot}02$)). During a mean follow up of 16 months five patients (20%) in group 3, 11 patients (35%) in group 1 ($p =$ NS), 15 patients (54%) in group 2 ($p < 0{\cdot}02$), and 10 patients (48%) in group 4 ($p < 0{\cdot}05$) developed cardiac events (angina, congestive cardiac failure, reinfarction, operation, or death).

Painless ST segment depression on exercise six weeks after myocardial infarction does not seem to reflect impairment of functional capacity or left ventricular function, or predict cardiac events.

Dynamic coronary stenosis in patients with single vessel coronary artery disease: implications for therapeutic intervention

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Alteration in coronary vasomotor tone may be important in the genesis of ischaemia in patients with single vessel coronary artery disease (SVD), and the role of β blockers in the treatment of such patients is controversial. We studied 10 patients (nine men) aged 34–75 (mean 50 years) with SVD. To detect the variability in the ischaemic threshold all underwent serial treadmill exercise testing at a similar time on three days while off all antianginal medications. Nine patients also underwent testing with ergometrine off treatment. Patients then entered a double blind, randomised crossover study of a β blocker (atenolol, 100 mg/day) and a calcium antagonist (nifedipine 10 mg three times a day). Assessment was by treadmill exercise testing, ambulatory ST segment monitoring, and angina diaries. All patients had a positive treadmill test when off treatment, eight had a positive test when on nifedipine, and five when on atenolol. Atenolol significantly prolonged the time to 1 mm ST segment change when compared with both nifedipine (8·7 *v* 5·6 mm, $p < 0.01$), and no treatment (8·7 *v* 5·0 mm, $p < 0.01$). Atenolol also reduced the total duration of ischaemia on ambulatory monitoring significantly more than nifedipine (22·4 *v* 59·0 min, $p < 0.05$). Two patients showed considerable variability during treadmill testing in time to ischaemia, and a further four patients had a positive ergometrine test. In this subgroup with objective evidence of altered vasomotor tone atenolol was again an effective treatment.

β Blockade is an effective treatment in patients with SVD, even when there is objective evidence of alteration in vasomotor tone.

An in vivo assessment of infarct size

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There is no reliable method of accurately estimating infarct size in the acute clinical phase of myocardial infarction. To assess the usefulness of perfusion imaging to provide an estimate of infarct size 20 small pigs (11·8–16·7 kg) had gated thallium scans performed before and after medial sternotomy as control. Myocardial infarction was produced by two stage occlusion of the left anterior descending coronary artery. Two, 4, 6, or 8 hours after infarction 60 MBq of thallium-201 was injected intravenously and scans gated to the electrocardiograms were attained in the anterior and 45° left anterior oblique projection. Infarct size was expressed as a percentage of the whole left ventricle as seen on the end diastolic image and as a mean of two views. Hearts were then extracted and counted whole, and the infarct size was estimated. The open left ventricle was counted from both the endocardial and epicardial surfaces and again infarct size was expressed as a percentage of the whole left ventricle. The infarct sizes measured from the opened left ventricle correlated well with those measured in the intact heart ($r = 0.93$). In vivo infarct size varied from 15% to 30% of the left ventricle. The infarct size estimated in vivo correlated well with both that of the opened left ventricle and the intact ventricle, but correlation with the intact ventricle was better ($r = 0.90$). Infarcts of greater than four hours' duration were successfully stained with tetrazolium and infarct weights correlated well with infarct scans.

In the pig model infarct sizing by gated thallium scans seems to be accurate. This technique can be performed in patients and promises to be a method of infarct sizing that can be used during the acute stage.

Doppler detected mitral regurgitation after myocardial infarction: relation to site of infarction and left ventricular function

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To assess the frequency and severity of mitral regurgitation (MR) in the chronic phase of myocardial infarction (MI) 80 patients had pulsed Doppler echocardiography with assessment of MR and radionuclide ventriculography with measurement of left ventricular ejection fraction (LVEF) both at a mean of 42 days after the onset of MI. MR was found in 14 (35%) of 40 patients in anterior MI compared with 17 (42%) of 40 patients in inferior MI (p = NS). MR was at least moderate in seven patients with anterior MI and in five patients with inferior

MI. Mean LVEF in patients with anterior MI and MR was 0·27 (0·07) and it was 0·38 (0·12) in those without MR (p < 0·005). When MR was at least moderate, mean LVEF was 0·22 (0·06) as compared with 0·32 (0·05) when MR was only mild (p < 0·005). For inferior MI mean LVEF in patients with MR was 0·41 (0·11) *v* 0·45 (0·10) in patients without MR (p = NS). There were no significant differences in mean LVEF between patients with at least moderate MR (0·37 (0·11)), mild MR (0·43 (0·11)), or no MR (0·45 (0·10)).

Mitral regurgitation is not uncommon after MI and its frequency in anterior and inferior MI is similar. Both its occurrence and severity in patients with anterior MI are related to depression of the LVEF. The mechanism of mitral regurgitation may be different in inferior MI since neither its occurrence nor its severity seemed to be related to the LVEF.

Low dose enoximone is haemodynamically effective in refractory heart failure

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The phosphodiesterase inhibitor enoximone has major inotropic and vasodilatory properties. Doses of between 3 mg/kg and 6 mg/kg have been used and were associated with appreciable side effects. We have studied the effectiveness of a lower dose of enoximone (100 mg) three times a day in 14 patients with refractory heart failure. Baseline values of cardiac index (CI), pulmonary capillary wedge pressure (PCWP), and pulmonary artery pressure (PAP) were measured with a thermodilution catheter. Systolic blood pressure (SBP) and heart rate (HR) were also measured. All these variables were measured again 1, 2, 4, 6, and 8 hours after 100 mg of enoximone and again at 24 hours after further doses of enoximone at eight and 16 hours. During the first eight hours, CI increased by 33% from a baseline of 2·07 l/min/m^2 (p < 0·022), PCWP decreased by 33% from a baseline of 23·28 mm Hg (p = 0·004), PAP decreased by 22% from a baseline of 35·92 mm Hg (p = 0·017), and RAP decreased by 41% from 9·43 mm Hg (p = 0·024). SBP and HR showed no significant change during this period. At 24 hours a 36% improvement in CI (p = 0·02), a 46% improvement in RAP (p = 0·013), and a 14% improvement in PAP were maintained (p = 0·025). PCWP, SBP, and HR showed no significant change from baseline at this stage. One patient had nausea.

Enoximone in low doses is haemodynamically effective and well tolerated.

Influence of platelets on arrhythmias and haemodynamic function during coronary occlusion

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To investigate the possible role of platelets in mediating the adverse effects of coronary occlusion we studied the occurrence of ventricular arrhythmias and systemic pressure during occlusion of the left anterior descending coronary artery (LAD) in rabbits with different states of platelet activation. In untreated controls (n = 10) ligation of the LAD produced immediate hypotension. Blood pressure fell by 17 (3·3) mm Hg at two minutes and ventricular fibrillation occurred in 50%. In animals pretreated with platelet antiserum (n = 8) platelets were reduced by 98% from 510 (14) × 10^9/l and LAD ligation caused less hypotension (a fall of 6 (0·6) mm Hg (p < 0·05 *v* control)) and ventricular fibrillation (25%). When platelet activating factor (acetylglyceryl ether phosphorylcholine) 1 µg/kg was given intravenously 10 minutes after the onset of LAD occlusion in seven separate control animals it produced immediate profound hypotension (a fall of 61 (5·8) mm Hg in all seven and VF in six). Pretreatment with platelet antiserum (n = 8) substantially blunted the hypotensive response to the platelet activating factor (a fall of 11 (2·1) mm Hg) and ventricular fibrillation in two (25%) (p < 0·05).

These results indicate that platelet activation may contribute to the haemodynamic and arrhythmogenic effects seen during early coronary occlusion.

The mechanism of shock in right ventricular infarction

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University Hospital of South Manchester, Manchester

Shock associated with right ventricular infarction is well recognised and with appropriate treatment the prognosis is good. The mechanism of shock in right ventricular infarction has been debated. We studied seven patients with clinical cardiogenic shock after transmural inferior myocardial infarction that persisted despite appropriate fluid volume replacement. All were in sinus rhythm. No patient had been taking

β blockers. All had indwelling pulmonary artery flotation catheters and femoral arterial lines. The mean right atrial pressure (21·3 (3·1) mm Hg) exceeded the pulmonary artery wedge pressure (16·9 (3·9) mm Hg). The average mean arterial pressure was 48·6 (12·1) mm Hg, mean cardiac index 1·34 (0·30) l/min/m^2, mean left ventricular stroke work index (LVSWI) 6·7 (3·5) gm/m^2, and right ventricular stroke work index (RVSWI) 0·2 (0·4) gm/m^2. After treatment with intravenous dobutamine and glyceryl trinitrate and varying combinations, mean arterial pressure increased to 82·7 (15·3) mm Hg ($p < 0{\cdot}01$ compared with baseline) and mean cardiac index to 2·73 (0·32) l/min/m^2 ($p < 0{\cdot}001$). The mean LVSWI increased to 27·6 (9·3) gm/m^2 ($p < 0{\cdot}01$) but mean RVSWI was unchanged at 0·5 (0·5) gm/m^2 ($p > 0{\cdot}01$). There was no significant change in heart rate, mean right atrial pressure (23·0 (2·8) mm Hg), or pulmonary artery wedge pressure (19·0 (2·7) mm Hg) after treatment.

Reversal of shock was thus associated with an increase in LVSWI but without a concomitant increase in RVSWI, which suggests that the probable mechanism of shock in right ventricular infarction is left ventricular dysfunction.

The hyperadrenergic heart syndrome

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Patients with palpitation caused by persistent and excessive sinus tachycardia in response to normal physiological activities have been called "hyperadrenergic" and it has been suggested that these features are the result of increased sensitivity of cardiac β receptors. We have compared the autonomic responses of eight hyperadrenergic (HA) women with those of seven normal women. Heart rate and blood pressure were measured supine and with 90° head-up tilt, and again after propranolol 0·2 mg/kg alone and propranolol with atropine 0·04 mg/kg. The response of heart rate to isoprenaline infusions (0·5–4 µg/min) was measured in supine subjects. Mean supine heart rate was 91·6 (14·3) beats/min in HA patients and 60·8 (4·2) beats/min in controls ($p < 0{\cdot}001$). Mean increase in heart rate on tilting was 53·9 (23) in HA patients and 28·8 (8·3) in controls ($p < 0{\cdot}001$). There was no significant difference in blood pressure between HA and controls and no significant change in blood pressure after tilting in either group. In the HA women mean plasma noradrenaline was 1·79 (0·77) nmol/l when subjects were supine and 4·72 (1·12) after tilting and 0·80 (0·78) nmol/l in supine controls and 1·83 (0·76) after tilting the controls (HA *v* controls, $p < 0{\cdot}005$, both supine and after tilting; and supine *v* tilting, $p < 0{\cdot}02$ in both groups). There was no difference in plasma concentrations of adrenaline between the groups. The increase in β blocked heart rate on tilting and with the addition of atropine was similar in HA women and controls. The increase in heart rate during isoprenaline infusion was 9·5 to 15·6 beats/min greater in HA women than in controls ($p < 0{\cdot}05$ at doses up to 1·5 µg/min).

These results suggest that HA patients have increased resting sympathetic tone and an exaggerated sympathetic reflex response to postural change.

Br Heart J 1988;**59**:639–40

Correspondence

Acceleration time in the aorta and pulmonary artery measured by Doppler echocardiography in the midtrimester normal human fetus

Sir,
I wish to take issue with Machado *et al* (1987;58: 15–8) who measured aortic and pulmonary artery acceleration times in a series of human fetuses and inferred that pulmonary vascular resistance was increased. They based this conclusion on studies in adults that showed that acceleration time is shortened in the pulmonary trunk when pulmonary mean pressure is increased.[1] Machado *et al* inferred that the fetal pulmonary vascular resistance is higher because acceleration times were slightly shorter in the fetal pulmonary trunk than the aorta.

The observation that flow profiles in the aortic and pulmonary circuits are different is not new; it was reported in the fetuses of sheep by Rudolph.[2] It is well known that aortic and pulmonary pressures are equal in the fetus and that fetal pulmonary vascular resistance is high. The precise relation of the vascular resistances of the aortic and pulmonary circuits has, to my knowledge, not been investigated in any animal model. Because the ductus is widely patent in utero the vascular resistance reflected by events in the pulmonary trunk, where Machado *et al* made their measurement, must have reflected the vascular resistance of the placenta (which is low) and that of the lower body of the fetus as well.

The original observation by Kitabatake *et al* assumes that acceleration time relates to mean pulmonary pressure and consequently vascular resistance.[1] There are other more complex factors which alter this measurement, including the vascular impedance, capacitance of the vascular bed in the distal circuit, the intrinsic contractile properties of the left and right ventricles[3] and the preload conditions of the two ventricles in the fetus. These factors may be quite different in the fetus and adult, and Machado *et al*'s inference that the acceleration time reflects higher pulmonary vascular resistance seems to be too simple.

It is well known that pulmonary vascular resistance in the fetus is high although pulmonary and aortic pressures are similar. Machado *et al* provide evidence only that there is a slight difference in acceleration times, with that of the pulmonary trunk measurement being shorter, without examining the factors affecting acceleration time which appear to be complex and affected by many physiological variables.

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This letter was shown to the authors, who reply as follows:

Sir,
Dr Silverman seems to have misunderstood the intention of our paper. Apparently he believes that we are saying something about the lung fields. But in the fetus the pressure in the main pulmonary artery reflects the cumulative resistance of the lung fields, the lower body of the fetus, and the placenta.

We found that the acceleration time in the pulmonary artery in the early human fetus was different from that in the aorta. Based on evidence from adults *and children* we felt this indicated a difference between the pressures in the two great arteries. We agree with Dr Silverman that alternative indices of cardiovascular function may account for our findings. Those he quotes are not measurable in the intact human fetus. Our interpretation is supported by further work by us that shows that later in pregnancy the acceleration times in both great arteries become equal; this is consistent with the fall in placental resistance as gestation advances. Conversely, when placental resistance is abnormally high the acceleration time in the pulmonary artery is abnormally short in late pregnancy.

He also makes the classic error of thinking that indices derived from the fetal animal model can in every respect be extrapolated to the intact human fetus. Recent research from many workers who looked at different aspects of the fetal circulation shows that this is not so.[1-6] His statement that "it is well known that aortic and pulmonary pressures are equal in the fetus" was reported only in the fetal lamb. The gestational age at which this relation was found is not clear nor is it known how gestation in sheep relates to human gestation in terms of fetal development.

Much work needs to be done in the study of the haemodynamic function of the human fetus. But we must keep an open mind on the findings and not jettison results that do not fit with preconceived ideas that are derived from work in a different species with quite evident developmental differences.

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Notices

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 22 to 24 November 1988. The closing date for receipt of abstracts has been changed to 24 June 1988 and is not as indicated in an earlier notice.

The Annual General Meeting for 1989 will take place in Oxford on 6 and 7 April 1989, and the closing date for receipt of abstracts will be 6 January 1989.

European-American cardiology in London

A combined course organised by the American College of Cardiology, British Cardiac Society, and European Society of Cardiology will be held in London on 1 to 3 June 1988. Inquiries from those residing in Europe to European Cardiology Congress Organization, European Society of Cardiology, Rue Juste Olivier 22, CH-1260 Nyon, Switzerland; from those residing in North America to Registration Secretary, Extramural Programs Department, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, MD 20814, USA.

International Union of Angiology

The 15th World Congress of the International Union of Angiology will take place in Rome from 17 to 22 September 1989. Inquiries to Professor Antonio Strano, Via di Vigna Stelluti 40, 00191 Rome, Italy.

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Br Heart J 1988;59:641–7

Survival of patients with mild angina or myocardial infarction without angina: a comparison of medical and surgical treatment

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SUMMARY A group of 390 patients with mild angina pectoris or myocardial infarction without subsequent angina had early coronary bypass operation. Five year survival was significantly higher (95·4%) than in a similarly selected medically treated group (88·5%) reported before. One death occurred in the 30 day postoperative period. Five year survival in the 179 patients who had internal mammary artery grafts was 98·9%. Survival for patients with mild angina and satisfactory left ventricular function (96·2%) was significantly higher than in the medical subset (91·3%).

In the patient population studied, five year survival was higher in patients who had early bypass operations than in those who did not.

The Coronary Artery Surgery Study has influenced selection of patients for coronary bypass surgery. The Coronary Artery Surgery Study randomised trial was confined to patients who had mild angina or myocardial infarction without subsequent angina.[1] The most unexpected finding was the high survival rate in the medical group ("surgery deferred contingent on worsening symptoms"). A subsequent report of the Coronary Artery Surgery Study "randomisable" patients (eligible for randomisation but not randomised because of decision by the patient or physician) showed similar results for the medical group, although the baseline characteristics of the medical subset differed considerably from those of the medical patients in the randomised study.[2] In another study of patients in the Coronary Artery Surgery Study registry who were not randomisable, in those with mild angina and satisfactory left ventricular function five year survival of both the medical and surgical patients was 95%.[3] Analysis of our medically treated patients selected by the Coronary Artery Surgery Study criteria for the same 46 month entry period showed lower five year survivals than those reported by the Coronary Artery Surgery Study for the whole group and for various subsets.[4] This result suggested that a group of similarly selected surgical patients might also have lower survivals than those reported by the Coronary Artery Surgery Study for surgical patients.

Patients and methods

The criteria for selection of medical patients were similar to the 18 entry criteria used in the Coronary Artery Surgery Study randomised study, with five minor modifications that were intended to increase clinical specificity.[4,5] These entry criteria were used in the present study, except that those patients estimated to have 50–69% narrowing of the left main coronary artery were included, as in the Coronary Artery Surgery Study.[1] In our study of medically treated patients, such lesions were grounds for exclusion because it was believed that the expected prognosis was worse than for disease of two or three arteries. An additional deviation was inclusion regardless of geographical residence. The practice of regular five year survival studies of the first 1000 patients who had elective pure coronary bypass surgery each year made 4000 records available for the years 1976–1979. These 4000 patients represent 41·3% of the patients who had such operations during those years. A computer program was written to match some of the Coronary Artery Surgery Study criteria and 1182 patients were eligible for review.

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Table 1 *Baseline variables in study groups (%)*

Variable	*A*		*B*		*C*		*All*	
Patient (No)		312		25		53		390
Age (yr):								
Mean		54		55		53		54
SD		7		6		9		7
Male	(301)	97	(25)	100	(51)	96	(377)	97
Angina (Canadian grading):								
None	(0)	0	(0)	0	(53)	100	(53)	14
I	(198)	64	(16)	64	(0)	0	(214)	55
II	(114)	37	(9)	36	(0)	0	(123)	32
Cigarette use:								
Present smoker	(160)	51	(10)	40	(19)	36	(189)	49
Non-smoker	(139)	45	(13)	52	(30)	57	(182)	47
Unknown	(13)	4	(2)	8	(4)	8	(19)	5
Reported history of:								
Hypertension	(102)	33	(9)	38	(14)	27	(125)	32
Previous MI	(110)	35	(16)	64	(53)	100	(179)	46
Heart disease in family	(188)	60	(11)	44	(28)	53	(327)	58
Congestive failure	(3)	1	(1)	4	(3)	6	(7)	2
Diabetes mellitus	(17)	6	(1)	4	(3)	6	(21)	5
Stroke	(1)	0	(0)	0	(1)	2	(2)	1
ASO	(35)	11	(1)	4	(5)	9	(41)	11
Medication at entry:								
Nitrites (long-acting)	(184)	59	(15)	60	(35)	66	(234)	60
β blocking	(93)	30	(8)	32	(11)	21	(112)	29
Digitalis	(15)	5	(3)	12	(7)	13	(25)	6
Antiarrhythmic	(12)	4	(1)	4	(13)	25	(26)	7
Anticoagulant	(19)	6	(1)	4	(11)	21	(31)	8
Antiplatelet	(6)	2	(0)	0	(0)	0	(6)	2
Thiazides	(33)	11	(7)	28	(6)	11	(46)	12
Other BP medication	(31)	10	(2)	8	(4)	8	(37)	10
Frusemide	(5)	2	(0)	0	(5)	9	(10)	3
Unknown diuretic	(0)	0	(0)	0	(0)	0	(0)	0
Lipid lowering	(30)	10	(4)	16	(4)	8	(38)	10
None of above	(79)	25	(4)	160	(6)	11	(89)	23
Diseased vessels (≥70% narrowing):								
One	(61)	20	(3)	12	(7)	13	(71)	18
Two	(114)	37	(6)	24	(24)	45	(144)	37
Three	(137)	44	(10)	64	(22)	42	(175)	45
Diseased vessels (≥50% narrowing):								
Single	(31)	10	(1)	4	(3)	6	(35)	9
Double	(90)	29	(4)	16	(14)	26	(108)	28
Triple	(191)	61	(20)	80	(36)	68	(247)	63
Proximal LAD disease (≥70% narrowing)	(117)	38	(11)	44	(16)	30	(144)	37
Left ventricular score[5]:								
Patients (No)		312		25		53		390
Mean		6		9		8		7
SD		1		2		2		2
5 (normal)	(144)	46	(0)	0	(0)	0	(144)	37
6 to 10 (slightly abnormal)	(162)	52	(19)	76	(47)	89	(228)	59
11 to 15 (abnormal)	(6)	2	(6)	24	(6)	11	(18)	5
Ejection fraction:								
Patients (No)		312		23		53		388
Mean		71		40		59		67
SD		9		9		12		13
≥0·50	(312)	100	(0)	0	(43)	81	(355)	92
0·35 to 0·49	(0)	0	(18)	78	(8)	15	(26)	7
<0·35	(0)	0	(5)	22	(2)	4	(7)	2
Systolic BP:								
Mean (mm Hg)		138		133		130		136
SD (mm Hg)		19		19		19		19
≥160 mm Hg (7)	(47)	15	(3)	12	(7)	13	(57)	15

Table 1 *Baseline variables in study groups (%) (continued)*

Variable	*A*		*B*		*C*		*All*	
Diastolic BP:								
Average (mm Hg)		84		83		82		84
SD (mm Hg)		9		10		10		9
⩾100 mm Hg (%)	(29)	9	(2)	8	(4)	8	(35)	9
ECG findings:								
Q wave MI (%)	(53)	17	(14)	56	(44)	83	(111)	29
? Q wave MI (%)	(30)	10	(3)	12	(9)	17	(42)	11
ST depression (%)	(101)	32	(12)	48	(7)	13	(120)	31
T wave abnormality* (%)	(118)	38	(23)	92	(41)	77	(182)	47
Conduction defect (%)	(8)	3	(5)	20	(1)	2	(14)	4
LVH	(7)	2	(1)	4	(0)	0	(8)	2
LA hemiblock	(5)	2	(1)	4	(0)	0	(6)	2
1° AV block	(1)	0	(0)	0	(0)	0	(1)	0
None of the above	(101)	32	(0)	0	(0)	0	(101)	26
Serum cholesterol:								
Patients (No)		311		25		52		388
Average (mg/dl)		6·95		6·80		7·00		6·95
SD (mg/dl)		1·31		1·31		1.29		1·31
⩾6·46	(195)	63	(15)	60	(28)	54	(238)	61

Group A: mild angina and ejection fraction ⩾0·50.
Group B:mild angina and ejection fraction <0·50.
Group C: myocardial infarction without subsequent angina.
*Diphasic or inverted T waves in leads in which T should be upright
MI, myocardial infarction; ASO, arteriosclerosis obliterans, LAD, left anterior descending artery; BP, blood pressure;
ECG, electrocardiogram; LVH, left ventricular hypertrophy; LA, left anterior; AV, atrioventricular.
Except where means (SD) are indicated, the numbers in parentheses are the size of the subgroup and the other numbers are percentages to the nearest whole number.

Because we restricted analysis to patients who had catheterisation at the Cleveland Clinic Foundation, 387 patients were excluded. The remaining 795 patient records were reviewed to ensure conformity with the entry criteria. Class 2 angina in our computer coding meant distress that was precipitated by walking one block or more on level ground, but in the Canadian grading system for angina pectoris, used by the Coronary Artery Surgery Study, grade II angina meant either ability to walk at least two blocks before precipitation of distress or conformity with certain other criteria.[6] Recoding the angina eliminated a large number of patients whose discomfort was too easily precipitated by walking to be classified as Canadian grade II. Additional patients were excluded on the basis of other Coronary Artery Surgery Study criteria and the final study group totalled 390 patients, approximately 15% of the patients who had pure bypass operations after catheterisation at the Cleveland Clinic Foundation.

Groups A and B in the Coronary Artery Surgery Study both had mild angina and were separated by the ejection fraction, when available. Group A had ejection fraction ⩾0·50 and group B <0·50. Group C (myocardial infarction without subsequent angina) patients had ejection fraction of at least 0·35.

Ejection fractions were not routinely calculated at the time of catheterisation, so films were reviewed and the ejection fraction was measured without knowledge of clinical or survival information. In two cases the films were not available, so assignment of both to group B was on the basis of the number of areas of the right anterior oblique ventriculogram that showed impairment of contractility, according to the practice used by the Coronary Artery Surgery Study.[5] Ventricular scoring was done by the Coronary Artery Surgery Study method. A score of 5 was normal, and scores of 6–10 and 11–15 represented mild and moderate left ventricular impairment, respectively. Electrocardiograms were recoded according to the Minnesota criteria, a modification of which was used by the Coronary Artery Surgery Study.[7]

Each patient was followed until death or for a minimum of five years from a date 16 days after catheterisation, because the mean interval between catheterisation and operation was 15·5 days.[2] No patient who met the criteria for entry into the study died during the 16 day interval or before planned operation. All deaths are included in the statistical analysis.

We used standard life table methods for univariate survival analysis.[8] Survival curves were compared by the generalised Wilcoxon statistic.[9] Significance levels of 0·05 or less were considered to be statistically significant. We used the Cox proportional hazard model for multivariate analysis[10] to test for survival differences in the two groups (medical, surgical). Baseline factors shown (*a*) to differ between the medical and surgical group and (*b*) to be related to survival were initially forced into the Cox model to adjust for any survival differences related to these differences in group characteristics. The difference in survival between the two groups was then tested.

Results

One of the 390 surgical patients died in the hospital of a transmural myocardial infarction; this was the only death that occurred within 30 days of operation. Definite transmural myocardial infarction was diagnosed postoperatively in eight patients (2·1%) and questionable transmural infarction in an additional three patients (total of 11 (2·8%)).

In some respects the baseline characteristics of the 390 surgical patients varied considerably from those of the 408 previously reported medical patients (table 1). Group C (myocardial infarction without angina) was smaller in the surgical group than in the medical (53 versus 111 patients), and this accounted for most of the difference in prevalence of myocardial infarction in the two groups. Group C was small because we are reluctant to advise operations in patients who are symptom free after myocardial infarction. Thiazide treatment was used in 12% of surgical patients and 20% of the medical patients. Narrowings of at least 70% in one, two, and three coronary arteries were found in 18%, 37%, and 45% of the surgical groups, respectively, and 36%, 40%, and 25% of the medical group. The proximal anterior descending artery (before any branches) was more commonly affected in the surgical patients than in the medical patients (37% versus 21%). Other baseline characteristics were similar in the medical and surgical groups.

Five year survival of surgical patients was not significantly different for the following subsets: age (<50 and ≥50 years), duration of symptoms (≤52 and >52 months), smoking before operation (yes or no), diabetes mellitus (yes or no), arteriosclerosis obliterans (yes or no), systolic hypertension (<160 and ≥160 mm Hg), diastolic hypertension (<100 or ≥ 100 mm Hg), serum cholesterol (<6·46 and ≥6·46 mmol/l), electrocardiogram (normal or abnormal), number of arteries affected (one, two, or three), left main artery 50–69% narrowed (yes or no), ejection fraction (<0·50 and ≥0·50), and clinical group (A, B, and C). Statistically significant differences were found for subsets identified by ventricular score (5, 6–10, and 11–15; p = 0·04); number of arteries affected in group A patients (one, two, and three; p = 0·05); and internal mammary artery graft (done or not done; p < 0·01). The five year survival of 179 patients who had internal mammary artery grafts as part of their operations was 98·9%, and it was 92% for those who had saphenous vein grafts only (p = 0·007). Survival was lower in the eight patients who had perioperative myocardial infarction than those who did not (75 and 96%; p = 0·005). The one postoperative death was caused by myocardial infarction; the five year survival of the seven who survived perioperative infarction was not significantly different from those who did not have myocardial infarction (p = 0·25).

The figure shows survival curves for surgical patients and for the medical group reported previously. Table 2 compares the five year medical and surgical survivals for the groups and for some subsets. Some of the subsets are small, so statistical comparisons are of doubtful meaning. Five year survival was 85% for 256 medical patients with multivessel disease and 95% for 319 surgical patients (p < 0·001). For those less than 50 years old medical and surgical survivals were not significantly different, but 44% of medical patients and 20% of the surgical group had single vessel disease. Multivessel disease in those aged less than 50 was associated with survival of 84% (70 patients) in the medical group and survival of 94% (78 patients) in the surgical group (p = 0·12). Survival of group A patients with multivessel disease was also higher (95% versus 88%) for the surgical group than for the medical group (p = 0·01).

Table 2 also shows survival of subsets of patients who had internal mammary artery grafts as part of their operation. Survival was higher for those who had internal mammary artery grafts than for the whole surgical group and for various subsets except for patients with single artery disease, all of whom survived. Survival of those patients less than 50 years old with multivessel disease was 100% if internal mammary artery grafting had been done (41 patients), compared with 84% (70 patients) for similar medical patients (p = 0·01).

We used a Cox model to compare the outcome of medical and surgical treatment, after adjusting for age, number of arteries significantly narrowed, ejec-

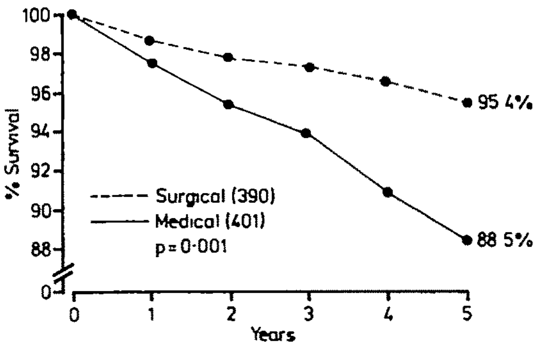

Fig *Survival curves of 401 patients treated medically initially and 390 who had early bypass surgery.*

Table 2 *Five year survival (%) of medical and surgical patients*

Group	*Medical* *All Patients*	*Surgical* *All Patients*	 *IMA*
Overall	89 (401)	95 (390) [0·001]	99 (179) [<0·0001]
Age:			
<50	90 (125)	95 (97) [0·34]	100 (51) [0·07]
≥50	88 (276)	96 (293) [0·0007]	98 (128) [0·0005]
ECG:			
Normal	93 (101)	98 (102) [0·09]	98 (51) [0·20]
Abnormal	87 (300)	94 (288) [0·004]	99 (128) [0·0003]
Number of vessels (≥70%):			
Single	95 (145)	100 (71) [0·14]	100 (38) [0·45]
Double	88 (159)	93 (144) [0·20]	98 (64) [0·01]
Triple	80 (97)	95 (175) [0·0001]	99 (77) [0·0002]
Proximal AD	83 (82)	95 (144) [0·003]	99 (65) [0·002]
Ejection fraction:			
<50	79 (46)	91 (33) [0·27]	100 (9) [0·40]
≥50	90 (353)	96 (355) [0·004]	99 (168) [0·0002]
Score			
5	95 (130)	99 (144) [0·12]	100 (70) [0·07]
6–10	86 (246)	94 (228) [0·01]	98 (103) [0·002]
11–15	76 (25)	89 (18) [0·33]	100 (6) [0·20]
Group:			
A	91 (267)	96 (312) [0·03]	99 (149) [0·003]
B	72 (25)	88 (25) [0·19]	100 (8) [0·11]
C	85 (109)	94 (53) [0·19]	100 (22) [0·17]
Group A: number of vessels			
Single	96 (111)	100 (61) [0·09]	100 (35) [0·21]
Double	91 (95)	93 (114) [0·68]	98 (55) [0·07]
Triple	85 (61)	97 (137) [0·002]	98 (59) [0·01]

IMA, internal mammary artery graft was a part of the surgical technique.

Proximal AD, anterior descending coronary artery narrowed ≥70% before any branches.

Number of patients are given in parentheses and p value of medical *v* surgical comparisons are in square brackets. See methods section for explanation of score.

Ejection fractions are missing in two medical and two surgical patients. See footnote to table 1 for definition of groups A, B, and C.

tion fraction, and electrocardiographic findings including myocardial infarction. There was a significant difference between the two treatment groups in five year survival ($p = 0·0002$).

Table 3 shows causes of death in the medical and surgical groups. Non-cardiac deaths in the medical group exceeded those in the surgical group, but the difference was not significantly different.

Discussion

The results of randomised prospective trials are best tested by repetition of the trial. Frequently this approach is practical, but in the case of coronary artery disease with mild angina pectoris or myocardial infarction without angina, repetition is not feasible. We are not questioning the validity of the Coronary Artery Surgery Study trial of treatment of mild angina or myocardial infarction without subsequent angina, but rather the clinical applicability of the survival findings. The Coronary Artery Surgery Study group recognised the problem and attempted to provide an answer by studying non-randomised patients in their registry.[23] Survivals were similar to those of randomised patients. Randomised trials and observational surveys cannot be compared directly even if meticulous attention is paid to duplication of entry criteria in the observational studies. The clinician interprets randomised trials in terms of the patients that he sees rather than as academic exercises, and usually would not apply the 18 entry criteria of the Coronary Artery Surgery Study to his patients. So the results of the trial may not be generally applicable. Because entry criteria can be uniform in an observational survey the results may more closely resemble those of a randomised trial than those of ordinary clinical experience. At least the reproducibility of survival results of non-randomised patients in the Coronary Artery Surgery

Table 3 *Causes of death (5 years)*

Cause	*Medical (401)*	*Surgical (390)*	*Total*
Myocardial infarction	30	9*	39
Congestive heart failure	3	1	4
Arrhythmia	1	0	1
Sudden	3	2	5
Non-cardiac	9	4	13
Unknown	0	3	3
Total	46	19	65

*Includes one postoperative death.
Numbers in parentheses are total number of patients followed up five years.

Study may be tested in an independent group of patients.

A study of patients who initially were medically treated, and selected on the basis of the Coronary Artery Surgery Study criteria for randomisation, showed lower survivals for the whole group and most subsets than similar patients of the Coronary Artery Surgery Study.[4] Lower survival might be caused by some unrecognised baseline variable, and surgical patients might also have lower survival, unless operation negated the influence of the variable. Lower survival after operation would influence the comparison with medical survival. In our comparison of medical and surgical results, survival was higher for surgical patients than for medical patients for the whole group and for all the subsets. The medical and surgical survival curves continue to diverge at five years. Subsets with high ventricular scores or low ejection fractions were small. Restriction of the analysis to patients with multivessel disease and ejection fraction of at least 0·50, as in the European Coronary Artery Surgery Study, showed significant difference in survival after medical and surgical treatment.[11] Survival rates for all subsets were higher in patients who had internal mammary artery grafts as part of their operative procedures than for those not stratified by operative procedure; except for patients with single artery disease, all of whom survived. A similar advantage for internal mammary artery grafts has been reported for patients selected on other bases.[12]

The Coronary Artery Surgery Study reported higher survival of surgical patients who had low ejection fractions than that of similar medical patients.[1] In the present study surgical survival was also higher, but the difference was not significant statistically, perhaps because of the small numbers of patients.

The 390 patients of this survey were selected from 4000 who had coronary bypass operations without additional procedures (valve operation, aneurysmectomy, etc). For many years the first 1000 such patients each year have been followed up every five years. The 4000 patients from the years 1976 to 1979 constituted 41% of eligible patients from the entire period. All had operation during the first five or six months of the year, but it is likely that they reflect the total experience. The 390 surgical patients in this survey were only a small percentage of the total patients having operation, but this was also true of the Coronary Artery Surgery Study investigation.[1]

This observational study suffers, just as the Coronary Artery Surgery Study "randomisable" study and all other observational studies do, from the questionable comparability of the different treatment groups. We have tried to address this issue by using statistical analyses that adjust for apparent group differences. One can never be sure that all confounding factors have been accounted for. The information gained from the careful analysis of observational data is still of interest and is sometimes the only recourse when a clinical trial is not feasible. In this case, we tried to test the clinical applicability of the results from a randomised prospective trial by matching the criteria for patient selection. Although survival was lower for our medical patients than that reported by the Coronary Artery Surgery Study, surgical survival was similar to that of the Coronary Artery Surgery Study and significantly higher than that of medical patients. The survival of our surgical patients is the same as that of the "randomisable" patients in the Coronary Artery Surgery Study if operative deaths (1 in 390 versus 7 in 570, respectively) are excluded.[2] The reason for the difference in survival of medically treated patients from that reported by the Coronary Artery Surgery Study is not apparent, but if it is ascribed to some unidentified difference in baseline characteristics these must have been nullified by operation. If survival of medically treated patients with mild angina and fairly normal ejection fractions is as high as reported by the Coronary Artery Surgery Study, the wisdom of advising early angioplasty or bypass surgery for improvement in prognosis in patients with mild symptoms might be doubted, unless differences in survival appear later. The lower survivals of our medically treated patients and those in the European Coronary Artery Surgery Study suggest that other studies of patients meeting the Coronary Artery Surgery Study criteria should clarify the clinical applicability of the results of the Coronary Artery Surgery Study.[11] Improved survival of surgical cases in which internal mammary artery grafting was part of the operative procedure means that future comparisons of medical and surgical treatment should include operative technique as a prognostic variable.

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Ventricular arrhythmias in long term survivors of orthotopic and heterotopic cardiac transplantation

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SUMMARY Fourteen long term survivors with orthotopic (recipient heart replaced by donor heart) and nine with heterotopic cardiac transplants (recipient heart retained) had 24 hour ambulatory electrocardiographic monitoring to detect ventricular arrhythmias. Arrhythmia was uncommon in the patients with orthotopic transplants; none of them had more than one extrasystole per hour. In the patients with heterotopic cardiac transplants the recipient's own heart showed significantly more frequent ventricular arrhythmias than the corresponding donor heart: abnormal complexes (mean/24 h) 4583 *vs* 42·7; extrasystoles 1772 *vs* 17·8; pairs 121 *vs* 0·8. There was no relation between the abnormal ventricular activity of the two hearts in the patients with heterotopic transplants on a beat by beat, hourly, or 24 hour basis. There was no consistent diurnal variation in the frequency of the abnormal ventricular beats after cardiac transplantation. The occurrence of ventricular arrhythmia was unrelated to the interval from operation to the study.

In long term survivors of cardiac transplantation the denervated heart shows a little ventricular ectopic activity even when compared with normal hearts. In patients with heterotopic transplants ventricular arrhythmias commonly occur in the recipient's own heart; these are probably related to the underlying severity of the original disease.

Ventricular arrhythmias during ambulatory monitoring have been reported to be more frequent in patients after conventional orthotopic cardiac transplantation than in normal subjects.[1-3] Most of these arrhythmias occur soon after the operation.[4] Little is known about their occurrence, possible causes, and potential influence on prognosis in late survivors of cardiac transplantation.[5]

The development of two channel electrocardiographic recorders and computerised analysers permits the separate identification of the QRS complexes of the two hearts (donor and recipient) after heterotopic cardiac transplantation and a quantitative simultaneous study of the ventricular arrhythmias of both hearts during Holter monitoring.

The purpose of our study was to (*a*) find out how common ventricular arrhythmia was in the denervated heart late after transplantation, (*b*) to assess whether ventricular arrhythmia was more common after heterotopic transplantation than after orthotopic transplantation, and (*c*) to compare the occurrence of ventricular arrhythmia in the denervated donor and innervated recipient hearts in patients with heterotopic transplants.

Patients and methods

Fourteen men with orthotopic (mean (SD) age 45 (8) years) and nine patients with heterotopic (eight men and one woman, age 42 (10) years) cardiac transplants were studied by ambulatory 24 hour electrocardiographic monitoring. Donor hearts were obtained from individuals aged 22 (7) years. The surgical techniques are described elsewhere.[6 7] The interval from operation to the study varied from six to 42 months (mean 20) in the orthotopic and from seven to 18 months (mean 11) in the heterotopic transplantation group. Most of the patients were taking a mixture of drugs (cyclosporin, azathioprine, prednisolone, aspirin, dipyridamole, and diuretic) but no patient was on an antiarrhythmic drug. All patients were symptom free, ambulant, and performing their

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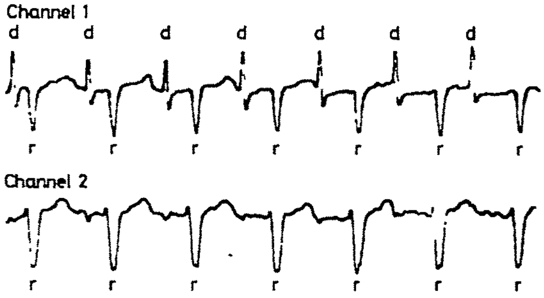

Fig 1 *Typical electrocardiographic trace from 24 hour Holter monitoring of a patient with a heterotopic cardiac transplant. Channel 1 · donor's (d) and recipient's (r) QRS complexes are clearly distinguishable Channel 2: recipient's (r) QRS complex is dominant.*

usual daily activities. Each patient kept a detailed diary of activity and symptoms. The most recent biopsy specimen was normal in 21 patients but two patients showed evidence of mild rejection.

ELECTROCARDIOGRAPHIC RECORDING

Ambulatory 24 hour electrocardiograms were recorded on Oxford Medilog II recorders with two channels. The skin was carefully prepared and electrodes were placed to record modified lead V1 and V4 in patients with orthotopic transplants. In patients with heterotopic transplants a modified V4R lead was recorded instead of V1 to permit better separation of the two QRS complexes. Because the donor heart lay to the right of the recipient heart its QRS complex was clearly delineated in V4R whereas in lead V4 the QRS complex of the recipient's own heart was dominant. Figure 1 shows a typical electrocardiographic trace from a patient with a heterotopic cardiac transplant.

ARRHYTHMIA ANALYSIS

We used a computerised template system (J Johnston, Oxford), based on a QRS pattern recognition that could classify QRS complexes into different families, to analyse the ventricular arrhythmias. The system consisted of a Z80A pre-processor and a DEC LSI-11 master. The normal QRS complex was defined by the operator and recognised by the system thereafter. Any unrecognised QRS complex was screened carefully by the operator and if its shape indicated a ventricular origin or abnormal ventricular conduction it was classified and subsequently recognised as an "abnormal complex". We used the following definitions: extrasystole, an abnormal complex with a coupling interval less than 80% of the previous RR interval; pair, two consecutive abnormal complexes; run, three or more abnormal complexes with a rate less than 120 per minute; ventricular tachycardia, three or more ventricular extrasystoles with a rate greater than 120 per minute. Figure 2 shows an example of ventricular extrasystoles from the donor and the recipient heart of a patient with a heterotopic transplant.

Every electrocardiographic tape from the group with heterotopic transplants was analysed twice and the dominant QRS complex on each channel was identified separately. In the heterotopic transplant group we attempted to correlate the frequency of the abnormal complexes and ventricular extrasystoles in the two hearts during the whole 24 hour period and also on an hourly basis. In addition, we attempted to study the possible temporal relation between individual extrasystoles in the two hearts

The times of waking up and sleeping were noted and the mean rates of abnormal complexes and extrasystoles during sleep and wakefulness were calculated in both groups.

Finally, in both groups we examined the severity of arrhythmia and the interval since operation to see whether there was a correlation.

STATISTICAL ANALYSIS

All data are expressed as mean values (1 SD). We used the paired or unpaired Student's t test and the non-parametric Wilcoxon test as appropriate.

Results

CLINICAL CHARACTERISTICS

Not surprisingly, the donor hearts were obtained from individuals who were younger than the recipients ($p < 0{\cdot}001$). The ages of the donors and

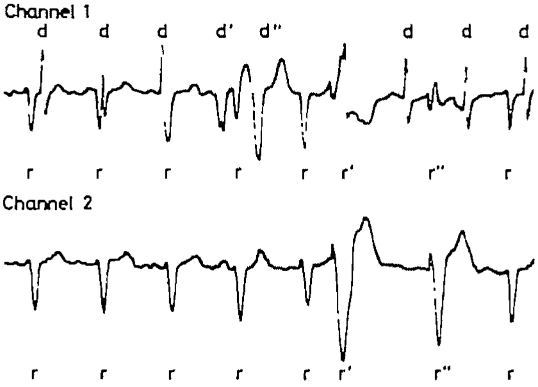

Fig 2 *Electrocardiographic trace of a patient with heterotopic cardiac transplantation with extrasystoles from both hearts. Channel 1: donor's (d) QRS complex is dominant. Channel 2: recipient's (r) QRS complex is dominant. d' and d", extrasystoles from donor's heart. r' and r", extrasystoles from recipient's heart.*

the recipients in the orthotopic and heterotopic transplant groups were not significantly different. The mean interval from operation to the study was longer in the orthotopic group than the heterotopic transplantation group ($p < 0·02$).

No symptoms were reported by patients during the 24 hour study period.

ARRHYTHMIAS

Tables 1 and 2 shows the number of the "abnormal complexes", extrasystoles, pairs, and runs in the two groups of patients. Ventricular tachycardia was not seen in any patient. Nine (39%) out of the 23 denervated hearts had no abnormal ventricular activity at all and in rest such activity was infrequent. This low occurrence of ventricular arrhythmia was similar in the donor hearts of both groups. We saw many abnormal complexes and extrasystoles in the recipient hearts of those patients with heterotopic transplants.

Analysis of the arrhythmia frequency in those with heterotopic transplants on a 24 hour or hourly basis showed no relation between the two hearts. The occurrence of an extrasystole in the one heart did not correlate with the presence of an extrasystole in the other heart.

Table 3 shows the frequency of abnormal complexes per hour during sleep and waking. Abnormal complexes were less common during sleep in four donor and two recipient hearts in the nine patients with heterotopic transplants. In the orthotopic group three of the eight patients with abnormal ventricular activity showed a decline in the frequency during sleep. The occurrence of extrasystoles during the 24 hour period was also reduced during sleep.

Finally, the occurrence of abnormal complexes or ventricular extrasystoles was unrelated to the time since operation in both the orthotopic and heterotopic groups.

Table 1 *Complexes with abnormal QRS shape and ventricular arrhythmias detected during 24 hour monitoring in patients with orthotopic cardiac transplants*

No	*Abnormal complexes*	*Extrasystoles*	*Pairs*	*Runs*
1	0	0	0	0
2	5	2	0	0
3	0	0	0	0
4	21	19	1	0
5	9	9	0	0
6	0	0	0	0
7	9	9	0	0
8	0	0	0	0
9	3	2	0	0
10	1	1	0	0
11	1	3	0	0
12	0	0	0	0
13	0	0	0	0
14	29	6	2	1
Mean	5 9	3 6	0 3	0 1

Discussion

We are unaware of any previous reports of Holter monitoring of ventricular arrhythmias in patients with heterotopic cardiac transplants. This is perhaps because patients with this type of cardiac transplantation (where the original heart is retained) are rare and it is difficult to separate the QRS complexes of the two hearts during ambulatory monitoring. We found that the occurrence of ventricular arrhythmias was similar in the donor hearts of patients with orthotopic and heterotopic transplantation, so differences in surgical technique and haemodynamic function do not seem to influence significantly the occurrence of ventricular arrhythmia. In contrast, the recipient hearts of the heterotopic transplantation group showed substantially greater ventricular arrhythmia, probably because of contributory factors such as the presence of severe coronary or myocardial disease, possible dysfunction of the autonomic regulatory pathways,[8-10] and surgical trauma.

Table 2 *Complexes with abnormal QRS shape and ventricular arrhythmias detected during 24 hour monitoring in patients with heterotopic cardiac transplants*

	Donor heart				*Recipient heart*			
No	*Abnormal complexes*	*Extrasystoles*	*Pairs*	*Runs*	*Abnormal beats*	*Extrasystoles*	*Pairs*	*Runs*
1	20	20	4	0	14608	3421	410	241
2	0	0	0	0	2337	860	23	0
3	4	4	0	0	41	35	6	0
4	8	8	0	0	18	18	2	2
5	0	0	0	0	19	17	0	0
6	0	0	0	0	222	200	0	0
7	11	11	3	0	2658	7599	90	91
8	4	2	0	0	25	13	0	0
9	337	115	0	0	11317	3788	563	318
Mean	42 7	17 8	0 8		4583†	1772†	121*	

Compared with the donor heart· *p < 0 05. †p < 0 01

Table 3 *Number of abnormal complexes per hour while patients were awake and asleep*

Heterotopic					*Orthotopic*		
	Donor		*Recipient*			*Donor*	
No of patient	*Awake*	*Asleep*	*Awake*	*Asleep*	*No of patient*	*Awake*	*Asleep*
1	1·3	0·1	256	1302	2	0·1	0·4
2	0	0	115	69	4	1·1	0·6
3	0·1	0·5	1·9	1·7	5	0·2	0·8
4	0·4	0	0·4	1·7	7	0·3	0·3
5	0	0	0·9	0·9	9	0·1	0
6	0	0	7·2	12·8	10	0	0·1
7	0·6	0·2	328	845	11	0·3	0
8	0·3	0	1·2	1	14	1·7	0·7
9	7·2	27	687	40			

Ventricular arrhythmias were uncommon in the denervated transplanted heart; they were no more common than in normal individuals.[11-13] Only one denervated heart in this series showed more than a hundred extrasystoles in 24 hours; again this is probably within normal limits. The infrequent occurrence of ventricular arrhythmias during continuous ambulatory electrocardiographic monitoring in patients after orthotopic cardiac transplantation accords with previous studies,[1 14] although in these patients arrhythmias were less vigorously measured.

Several factors may be implicated in the arrhythmogenesis after cardiac transplantation. Supersensitivity to circulating catecholamines,[15] rejection episodes, and accelerated atherosclerosis[16] could favour the production of arrhythmia in the donor heart. But the low frequency of extrasystoles implies that such factors have a limited role. In the innervated hearts of the heterotopic group severe underlying disease (coronary artery disease, congestive cardiomyopathy) is the most likely cause for the increased numbers of arrhythmias. The lack of correlation between the arrhythmia in the donor and recipient heart underscores the importance of the different aetiological factors causing extrasystoles. In addition, the absence of simultaneous occurrence of arrhythmia indicates either lack of effect of the stimuli common for both hearts, such as hormonal factors and physical activity, or different bases for these stimuli in each heart.

Unlike normal subjects[17] we found no overall reduction in extrasystoles during sleep. Denervation of the donors' hearts and autonomic dysfunction[12-14] of the severely diseased recipient's own hearts might be responsible for the absence of a diurnal variation. It was interesting that some of the denervated donor hearts did show a reduction in extrasystoles during sleep; this probably reflects the lowered plasma catecholamines seen during sleep, with perhaps some added amplification caused by denervation supersensitivity.

Despite the frequent occurrence of extrasystoles in the recipient heart our patients did not report dizziness or palpitations. This presumably reflected the relatively small contribution of the recipient heart to total cardiac output.

Our study is limited by the short duration (24 hours) of electrocardiographic monitoring, since there is a significant day to day variability in the frequency of extrasystoles in patients with innervated hearts[18]; there is no information on such variability after cardiac denervation. The generally low occurrence of arrhythmia suggests that there will be less day to day variation in counts.

In conclusion, ventricular arrhythmias were no more common in donor hearts than in normal individuals. In contrast, the very high occurrence of ventricular extrasystoles in recipient hearts was probably related to their underlying severe disease. There was no evidence of simultaneous arrhythmia in both recipient and donor hearts.

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The reliability of measuring left ventricular ejection fraction by radionuclide cardiography: evaluation by the method of variance components

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SUMMARY A statistical model based on the method of variance components was applied to obtain confidence statements for single and repeat determinations of left ventricular ejection fraction by radionuclide techniques. With this approach variance caused by individual factors in the measurement procedure is estimated to allow calculation of confidence intervals based on single measurements and the detection limits for changes. Six study groups made up of a total of 143 subjects were examined by both multigated equilibrium and first pass imaging. Under favourable conditions (with an updated gamma camera and experienced observer) the 95% confidence interval with a single measurement of left ventricular ejection fraction by equilibrium imaging was ± 3 ejection fraction units, compared with ± 6 units with the first pass technique (one ejection fraction unit = 1/100 of the possible values from 0·00 to 1·00). The minimal significant changes (at the 5% level) in *measured* equilibrium left ventricular ejection fraction at intervals of 15 min, 3 days, 1, 3, and 4 weeks were ± 4, ± 4, ± 5, ± 5, and ± 6 units, respectively. The corresponding minimal detectable changes in a subject's "*true*" left ventricular ejection fraction for the same intervals were ± 7, ± 7, ± 10, ± 10, and ± 12 units respectively. With first pass imaging, only average values for the variation at repeat determination could be calculated. The minimal significant change in measured first pass left ventricular ejection fraction was ± 7 units, and the minimal detectable change in "true" left ventricular ejection fraction was ± 14 units. Measurements of left ventricular ejection fraction by equilibrium technique were generally more reproducible than first pass determinations because the variability caused by study acquisition, observer analysis, and residual errors was smaller.

The method of variance components appears to be well suited to the evaluation of quantitative biological measurements in clinical use. The popularity of established procedures may obscure the lack of basic information about method evaluation.

Promising new quantitative laboratory methods are often evaluated by standard statistical techniques that cannot answer the questions that are most relevant to the routine clinical application of the new method. When radionuclide techniques are used to measure the left ventricular ejection fraction the crucial questions are: if the ejection fraction is measured once in a patient what is with 95% probability the "true" ejection fraction of the patient? And what changes in the ejection fraction can be detected at repeat determination after an hour, a day, a week, or a month? To answer these questions, we have applied a statistical approach that has rarely been used in medical studies to a comprehensive analysis of measurements of left ventricular ejection

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fraction by multigated radionuclide equilibrium imaging, and we have examined some aspects of the variability of measurements obtained by the gated first pass technique. The mathematical description of this method of variance components has been reported elsewhere.[1] In the present paper we shall concentrate on the clinical aspects of the assessment.

Patients and methods

STUDY POPULATION

Data sets were collected from six study groups made up of a total of 143 subjects (aged 29–73 years) who gave their informed consent to the study. There were 14 healthy volunteers who were examined with approval of the Copenhagen County Scientific-Ethical Committee. The patients that we studied all had heart disease.

Group 1 was 29 patients with coronary artery disease examined by both equilibrium imaging and contrast ventriculography in order to determine the accuracy of the radionuclide method. Three inexperienced observers carried out the data processing of the radionuclide studies; one of them repeated the analysis later. The cineventriculograms were analysed in duplicate by an experienced radiologist.

Group 2—Twenty seven patients were randomly selected from groups 1 and 3. In all of them one equilibrium study was followed immediately by another. The two examinations were carried out by two inexperienced observers who positioned the camera and patient and did the subsequent computer processing of the acquired data.

Group 3 was made up of 21 patients with ischaemic heart disease or chronic heart failure or both. They had two equilibrium imaging examinations 1–3 days (median 3) apart, and all data processing was performed by one inexperienced observer.

Group 4 consisted of 19 patients: 10 with previous myocardial infarction, seven with ischaemic heart disease, and two with arterial hypertension. The variation in left ventricular ejection fraction within the same hour was examined by performing four successive equilibrium studies, which were started every 15 minutes. The patients also had first pass and equilibrium imaging performed at the same time of the day at intervals of one, three, and four weeks. Data processing in this group was undertaken by an experienced observer. Data were complete for 16 of the 19 patients.

All patients in groups 3 and 4 were considered to be clinically stable and their medications were not changed during the study period.

Group 5—Four normal subjects and 30 patients with previous myocardial infarction were examined only once by equilibrium imaging. Data were processed twice by both a medium and a highly experienced observer for comparison with the results obtained by the inexperienced observers in group 1.

Group 6 consisted of 10 normal subjects and 30 patients with recent myocardial infarction who were examined once by first pass and then immediately afterwards by equilibrium imaging. Data were processed by two highly experienced observers to compare the accuracy of first pass with that of equilibrium determinations and to measure inter and intra observer variation with the two methods.

RADIONUCLIDE CARDIOGRAPHY

Gated equilibrium imaging

In all the studies we used red blood cells labelled with stannous pyrophosphate and 20–30 mCi (740–1110 MBq) ^{99m}TC-pertechnetate. In vivo labelling was used in groups 1, 2, and 3; and in vitro labelling in group 4. We used a modified in vivo/in vitro technique[2] in groups 5 and 6. An individual left anterior oblique view (25°–45°) was used in all studies to give the best separation of the left ventricle from other heart chambers. In groups 1, 2, and 3, 24 frames were obtained per RR interval in a 32 × 32 word matrix and a total of three million counts were collected with a single crystal gamma camera equipped with a low energy (140 keV), high resolution, parallel hole collimator. In groups 4, 5, and 6 data were acquired in a 64 × 64 word matrix and five million counts were collected in 20 (groups 4 and 5) or 32 frames (group 6) with an updated version of the same gamma camera. All data were obtained with the patients in the resting supine position. In groups 3 and 4 the angulation of the gamma camera was noted initially in each patient and reused in the repeat studies.

Under these conditions and after background correction and standardisation as 20 frames per RR interval for all studies, the recorded activities from the left ventricular region of interest in the end diastolic frame were on average approximately 21 000 counts with in vivo labelling, 32 000 counts with in vitro labelling, and 17 000 with the modified in vivo/in vitro technique. These figures, however, are not directly comparable because they are influenced by the size of the patient, the size of the left ventricle, and the proportion of high activity structures (such as the spleen) in the field of view. The stability of red cell labelling was examined in the in vitro groups by comparing the concentration of activity in two blood samples drawn at an interval of 45 minutes and counted on the collimator surface with correction for delay and radiation decay. The average blood activities in the two series of samples were 17·87 and 17·01 cps/ml, corresponding to a calculated biological half time of approximately 10·5 hours.

Data were initially stored on floppy discs and later analysed by a dedicated medical computer system. The ejection fraction (EF) was calculated according to the general formula:

$$EF = \frac{EDC - ESC}{EDC},$$

where EDC and ESC are the background corrected end diastolic and end systolic counts respectively. The outline of the left ventricle was defined by a semiautomatic edge detection algorithm. Resultant end diastolic and end systolic regions of interest were visually inspected and manually corrected whenever inaccuracies were noted. In groups 1, 2, and 3 we used a background region of interest situated inferolateral to the left ventricle in the end systolic frame, avoiding high activity structures (aorta, spleen, and gastric wall). In groups 4, 5, and 6 we used a similarly located area that contained only the pixels with lowest activity during three successive systolic frames (end systolic frame ± one).[3]

First pass imaging

The first pass studies (groups 4 and 6 only) were performed as previously described[3] with the gamma camera in a standard 30° right anterior oblique position and before the multigated studies. In short, left ventricular ejection fraction was measured after gated reframing (16 frames per RR interval) of the original first pass data that were collected in list mode with R wave trigger marks. The left ventricular outline was drawn manually on composite pictures representing end diastole and end systole respectively. For background correction we used a crescent shaped region of interest drawn along the apical border of the left ventricle on the composite end systolic picture. Left ventricular ejection fraction was calculated from the dual background corrected time-activity curves generated from the left ventricular end diastolic and end systolic regions of interest. We used the maximal activity of the diastolic region curve for end diastolic counts and the minimal activity of the systolic region curve for end systolic counts.[3] With bolus injections of 20 mCi (740 MBq) of ^{99m}Tc left ventricular counts in the end diastolic frame were on average 2620 (range 860–4398) after background subtraction.

Ejection fraction unit

Left ventricular ejection fraction is a fraction, but is commonly expressed as a percentage. The term percentage is ambiguous when applied to changes in left ventricular ejection fraction. For this reason we give all confidence statements and changes in left ventricular ejection fraction in "ejection fraction units" (one unit is 1/100 of the theoretical range from 0·00 to 1·00).

CINEVENTRICULOGRAPHY

In group 1 single plane angiograms (50 frames/s) were obtained in the 30° right anterior oblique projection after injection of 45 ml of Urografin 370 (meglumine diatrizoate (66%) and sodium diatrizoate (10%)) at 12 ml/s. The end diastolic and end systolic outlines, including papillary muscles and trabeculations, were traced and the volumes were calculated by the area-length principle[4] with a digitiser. One observer measured the left ventricular ejection fraction twice, at an interval of several months, on the original film. On each occasion the end diastolic and end systolic frames were identified by drawing the respective provisional ventricular outlines. The film was wound to and fro to ensure that these were the largest and smallest perimeters.

STATISTICAL ANALYSIS

Regression analysis per se was not part of the variance component model. It was carried out, according to the least squares principle,[5] to examine the accuracy of the two radionuclide methods and to allow this to be compared with the results obtained by other methods. Possible deviation from the line of identity was tested for by an F test,[5] and we used both the paired t test and Pratt's non-parametric test for paired samples[6] to test for differences between left ventricular ejection fraction values measured by the radionuclide and reference method.

Method of variance components

We examined the separate elements that may contribute to the total variability of the measurement of left ventricular ejection fraction. One measurement of left ventricular ejection fraction (X) was regarded as being made up of:

$$X = \xi + \Delta_{time} + \Delta_{acq} + \Delta_{obs} + \Delta_{res},$$

where ξ is the normal current level for X, Δ_{time} the "error" introduced by replacing the general true value by the actual value at the time of acquisition, Δ_{acq} the error introduced by replacing the "true" value ($\xi + \Delta_{time}$) by an examination value (*x* ray or radionuclide), Δ_{obs} the error caused by the observer's analysis of the acquired study, and Δ_{res} the residual error—that is the error not accounted for by any of the above. The four Δs were assumed to be independent with a mean value = 0 and the following variances: τ^2 for Δ_{time}, ($\tau \sim \tau$ime), α^2 for Δ_{acq} ($\alpha \sim \alpha$cquisition), ω^2 for Δ_{obs} ($\omega \sim \omega$bserver), and ρ^2 for Δ_{res} ($\rho \sim \rho$esidual). We have attempted to estimate the different values for these variances and their corresponding standard deviations (*a*) when left ventricular ejection fraction was measured by *x* ray or radionuclide technique; (*b*) if the observer was experienced or less experienced; and (*c*) if the gamma camera was old or new.

Results

Below we give the results of the regression analyses and the main outcome of the variance component model. All results of this model were originally calculated as variances. We give them in round figures as the more familiar standard deviations (SD), which are easier to interpret because they are expressed in ejection fraction units. It should be remembered, however, that an SD derived from several sources of error is the square root of the sum of the respective variances not the sum of the separate SDs.

LEFT VENTRICULAR EJECTION FRACTION BY MULTIGATED EQUILIBRIUM IMAGING

Accuracy.—The sets of values obtained by the two methods were not significantly different (paired t test, $p \approx 0{\cdot}64$; Pratt's test $p \ngtr 0{\cdot}10$). The regression line for cineventriculography (x axis) and equilibrium imaging (y axis) (fig 1a) was not significantly different from the opposite regression line (equilibrium technique (x axis) and cineventriculography (y axis)), and neither line differed significantly from the line of identity.

Intraobserver variation.—The variation in duplicate processing by the same observer of the same stored patient studies was larger with cineventriculography (fig 2a) than with equilibrium imaging (fig 2b) (SD ≈ 4·4 compared with 1·9). With the new gamma camera and greater observer experience the intraobserver variation at reanalysis was reduced to an SD of 1·1 for an observer of medium experience and of 1·0 for an observer of great experience.

Interobserver variation.—The variation found when the same radionuclide studies were reanalysed by different observers—or the "variability of judgment"—that is the sum of observer and residual variances also decreased, from SD ≈ 2·5 for an inexperienced observer with the older gamma camera to 1·9 for a more experienced observer and 1·1 for a very experienced observer, both with the new gamma camera.

Acquisition variation.—This was studied for only the older camera. Two inexperienced observers performed two equilibrium studies immediately after one another in the same patients. We found an SD of approximately 0·8, which was substantially lower than with cineventriculography. The SD for cineventriculography was not determined separately, but the combined SD attributable to acquisition plus observer variation was about 6·9. When the same gamma camera angulation was used for all studies in the same patient the acquisition SD was reduced to less than 0·3.

Reliability.—Left ventricular ejection fraction measured by *x* ray was equal to the radionuclide measurement (±1·96 SD) when the SD was calculated from the total (*x* ray + radionuclide) variability of a single measurement. This composite SD was ≈8·6 for an old camera and inexperienced observer, ≈ 8·4 for the new camera and more experienced observer, and ≈ 8·3 for new camera and a highly experienced observer. In all three instances

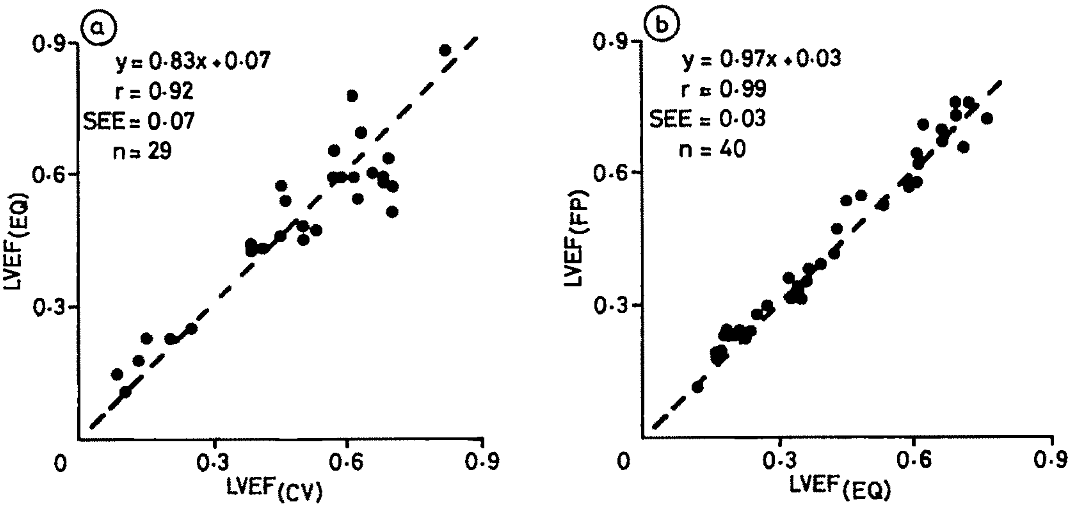

Fig 1 *Relation between values for left ventricular ejection fraction (LVEF) measured (a) by single plane cineventriculography (CV) and equilibrium imaging (EQ) and (b) by equilibrium (EQ) and first pass (FP) technique. Dotted lines indicate the line of identity.*

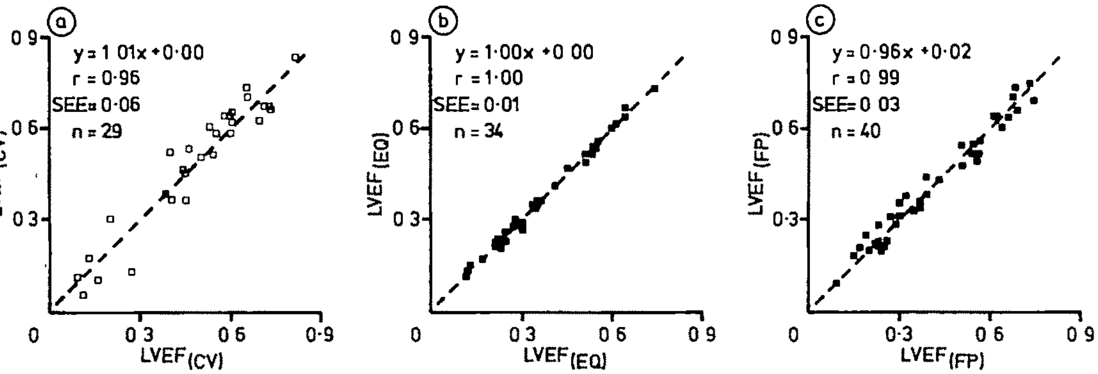

Fig 2 *Intraobserver variation at recalculation of left ventricular ejection fraction (LVEF) from patient studies obtained by (a) cineventriculography (CV), (b) equilibrium imaging (EQ), and (c) first pass technique (FP). Dotted lines indicate the line of identity.*

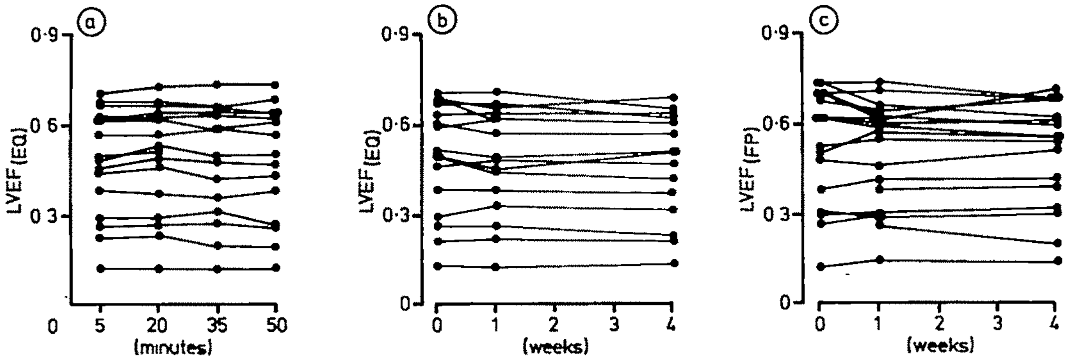

Fig 3 *Variations in left ventricular ejection fraction (LVEF) for repeat measurements at different times by equilibrium imaging (a and b) and by the first pass technique (c).*

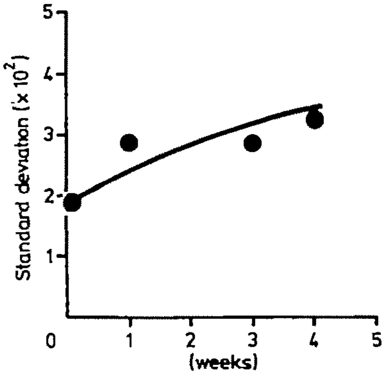

Fig 4 *The standard deviation as a function of time at repeat measurement of left ventricular ejection fraction by equilibrium imaging.*

the SD was almost entirely attributable to radiological variation.

Variation with time.—At re-examination there were insignificant differences in heart rate and mean arterial blood pressure. Mean (SD) measured

Table 1 *Estimated 95% confidence limits for single measurements of left ventricular ejection fraction (LVEF) by equilibrium (Eq) and first pass (Fp) imaging*

Method	*Camera*	*Observer experience*	*95% confidence interval*
Eq	Old	Low	Measured LVEF ± 5 EF units
Eq	New	Medium	Measured LVEF ± 4 EF units
Eq	New	High	Measured LVEF ± 3 EF units
Fp	New	High	Measured LVEF ± 6 EF units

EF, ejection fraction.

Table 2 *Minimal significant changes in* measured *radionuclide left ventricular ejection fraction (LVEF) and minimal detectable changes in* "true" *LVEF (figures in parentheses) at repeat determination at different times*

Radionuclide technique	*Gamma camera*	*Same observer*	*Observer experience*	*Interval between two studies* *1 hour*	*3 days*	*1 week*	*3 weeks*	*4 weeks*
Equilibrium	Old	No	Low	±7 (13)	±7 (13)	±8 (15)	±8 (15)	±9 (14)
Equilibrium	New	No	Medium	±6 (11)	±6 (11)	±7 (13)	±7 (13)	±8 (14)
Equilibrium	New	No	High	±4 (7)	±4 (7)	±6 (10)	±6 (10)	±6 (12)
Equilibrium	Old	Yes	Low	±6 (11)	±6 (11)	±7 (13)	±7 (13)	±8 (14)
Equilibrium	New	Yes	Medium	±4 (7)	±4 (7)	±6 (11)	±6 (11)	±7 (12)
Equilibrium	New	Yes	High	±4 (7)	±4 (7)	±5 (10)	±5 (10)	±6 (12)
First pass	New	No	High					±8 (15)
First pass	New	Yes	High					±7 (14)

With first pass imaging only an average value for the variation at repeat determination could be calculated. Consequently only one set of values (placed in the 4 weeks' column) is given for this technique.

equilibrium left ventricular ejection fraction was 1 (1) (range 0–5) for reacquisition within the same hour and 3 (2) (range 0–7) after four weeks (fig 3a and b). There was a clear tendency for increasing variation with time (fig 4).

Confidence statements.—Table 1 gives the 95% confidence intervals for single measurements. Table 2 lists the values of the minimal significant changes in *measured* left ventricular ejection fraction and the minimal changes in "*true*" left ventricular ejection fraction that could be detected with 95% confidence at repeat determination at different intervals.

LEFT VENTRICULAR EJECTION FRACTION BY FIRST PASS IMAGING

For the evaluation of this technique we included only values for left ventricular ejection fraction measured by the new camera and study analysis performed by two highly experienced observers.

First pass left ventricular ejection fraction values were on an average 1 ejection fraction unit higher than equilibrium left ventricular ejection fraction (range −4 to +9, $p < 0.01$), with the regression line deviating slightly from the line of identity (fig 1b). The variability was generally higher than with

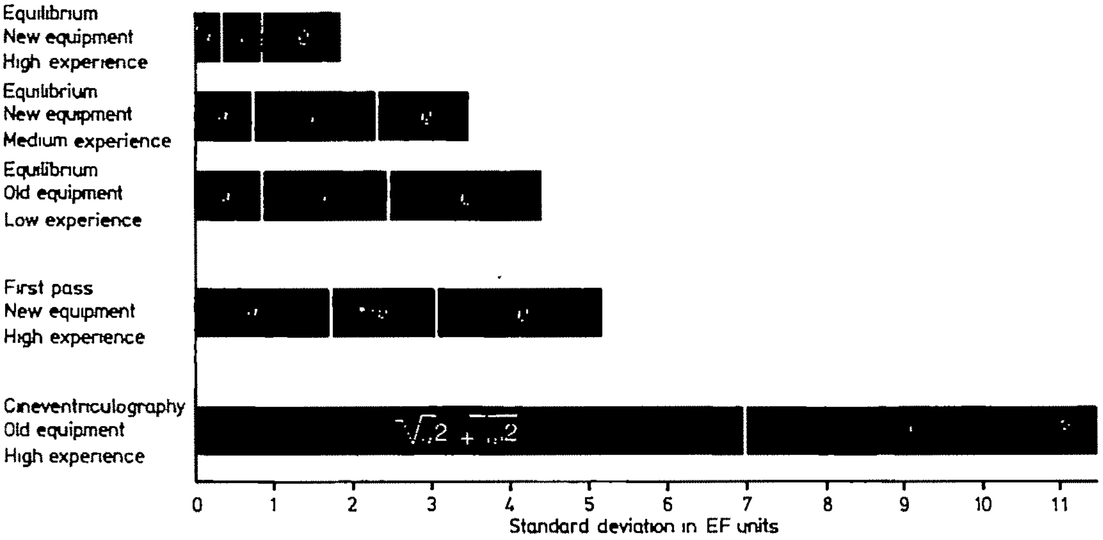

Fig 5 *Graphic representation of standard deviations attributable to study acquisition (α), observer analysis (interobserver variation) (ω), and residual errors (intraobserver analysis) (ρ) with the three methods of measuring left ventricular ejection fraction. α and ω were not determined separately for cineventriculography. Standard deviations attributable to the time variation are not shown because they were calculated only for the equilibrium method.*

equilibrium imaging. Thus the standard deviations of first pass acquisition, observer, and residual variances were 1·7, 1·3, and 2·1, respectively, compared with equilibrium worst case and best case figures of 0·8, 1·6, 1·9, and 0·3, 0·5, 1·2 respectively, and compared with the much greater radiological variances (fig 5), in which, for example, there was an observer SD of 4·3. The reliability was: equilibrium left ventricular ejection fraction = (first pass left ventricular ejection fraction − 1) ± 7 EF units.

Table 1 gives the confidence interval for single determinations of the left ventricular ejection fraction measured by the first pass technique. Table 2 gives the average detection limits at repeat measurement within four weeks.

Discussion

In method comparison studies many workers often use correlation analysis without considering whether this is a valid approach. As Altman and Bland pointed out,[7] the correlation coefficient does not measure agreement; it measures association. When two methods are compared the correlation coefficient depends on the range of the true values and the measurement errors of both methods. If the range of values is wide compared with the measurement error the r value will be high, whereas if the range is narrow and the methods are imprecise the correlation will be low.[7]

Another commonly misused technique is linear regression analysis; testing the slope of the regression line against zero is equivalent to testing the correlation coefficient.[7] With the least squares principle there is a tendency for the slope to be underestimated, and in addition many ignore the error inherent in any measurement of either dependent or independent variables. To compensate for this, we carried out the regression analysis twice, first using *x* ray left ventricular ejection fraction as the dependent variable, and then with radionuclide left ventricular ejection fraction as the dependent variable. We used regression analysis to examine the accuracy of both radionuclide methods so that our results could be compared with previously published results.

Other and more simple approaches have been proposed for method comparison studies[7] because linear regression is not suitable for estimation of the relative precision of the methods compared. Instead we used a variance component model. Before discussing the application, we review other reports on the evaluation of radionuclide measurements of left ventricular ejection fraction.

PREVIOUS INVESTIGATIONS

Correlation coefficients in studies that compared first pass left ventricular ejection fraction with single plane cineventriculography range from 0·79 to 0·97 (mean 0·89).[8–17] The few reported standard errors of the estimate (SEE) range from 3 to 8 ejection fraction units (mean 6 units).[8 9 11–14 17] In studies to compare multigated equilibrium imaging and single plane ventriculography the average r value was 0·84 (range 0·70–0·92),[10 12 16 18–21] and values for SEE were 11, 5, and 7 units.[12 19 21] Comparisons with biplane ventriculography gave an r value of 0·94 (SEE 7) with the first pass technique,[22] and values of 0·88 (SEE 6) and 0·93 with the equilibrium method.[19 23]

It is difficult to compare the reported results on reproducibility. The radionuclide methods differ considerably,[24] and the variability of repeat assessments is influenced by the selection of patients and by the proportion of patients with normal left ventricular ejection fractions.[16] Some studies are small,[11 25] and most deal with only a few aspects of reproducibility.[11 19 20 25–29] There is a tendency to use the same incorrect methods, and variability is expressed in various ways without taking into account all the contributory factors. This precludes the calculation of the relevant confidence intervals and detection limits. It is seldom stated how mean differences between sets of values were calculated, with sign or as the average numerical difference, or if a mean difference of X% was the percentage of an ejection fraction value or the difference expressed in ejection fraction units. Even more elaborate studies[16 28] use conventional methods that cannot give estimates that answer the most pertinent questions.

PRESENT INVESTIGATION

Because we cannot measure true left ventricular ejection fraction we cannot be certain that a method is accurate if there is no standard with which to compare it. What we can do is to compare two methods, which we believe measure what they are intended to do, and if we find "sufficient" agreement we postulate that they are accurate. The degree of disagreement that is tolerated is determined arbitrarily.

In the present study we found no statistical differences between equilibrium imaging left ventricular ejection fraction and angiographic left ventricular ejection fraction by linear regression or by two tests for matched pairs. On the basis of these results we decided that the radionuclide method was accurate. The outcome of the regression analysis was similar to that which has been reported by others.[10 12 16 19 21] We assumed that the two methods measured the same variable, albeit with different precision. Because the variability of the radiological method was so much greater (fig 5) it seemed irrelevant to calculate and use for later corrections an equation that expressed the "reliability" of the radionuclide method—that is its ability to predict the corresponding radiological left ventricular ejection fraction. Figure 1 shows that the variability of equilibrium imaging left ventricular ejection fraction was independent of the absolute magnitude of left ventricular ejection fraction. Consequently, all variances, changes, etc, were given in absolute figures. It seemed inappropriate to express the variability of ejection fraction determinations as the coefficient of variation, because this relates the standard deviation to the mean value, which may be unrepresentative of the individual patient.

First pass values were on average one unit higher than equilibrium imaging left ventricular ejection fraction, in accordance with the finding in a previous study.[3] This minor discrepancy might reflect differences between methods in background correction and delineation of the aortic valve plane.

With the variance component model we could demonstrate changes in variability when the circumstances of measurement were changed. For single determinations of left ventricular ejection fraction the 95% confidence interval fell from ±5 ejection fraction units with the old camera and an inexperienced observer to ± 3 units with the new camera and an experienced observer (table 1). Because the variability of the first pass method was usually higher (fig 5) the confidence interval with new equipment and an experienced observer was wider than for equilibrium imaging with an old camera and an inexperienced observer (table 1).

The reliability of measuring changes in ejection fraction by a particular method may be judged in two ways. Both depend upon (*a*) the inherent variability of the measurement procedure and (*b*) what is judged to be, in advance, the acceptable frequency of false positive results, for example 5%. Firstly, with repeat measurements what change in *measured* left ventricular ejection fraction is statistically significant (at the 5% level)—that is, should arouse the suspicion that a real change might have taken place between two measurements? We found that the necessary change in measured left ventricular ejection fraction was > 1·96 SD. For example, table 2 shows that when the same observer of medium experience uses the new camera for two studies at an interval of four weeks then a change of ⩾ 7 units in left ventricular ejection fraction is significant. Secondly, if the *"true"* left ventricular ejection fraction of a patient really changes between the two measurements, how large does the change need to be for it to be detected? This is partly determined by the number of false positives that we can accept. In the example chosen (table 2, 4 week column), it means that if we cannot accept more than 5%, observers of medium experience will not discover a change of ±11 units, whereas they will probably recognise changes of ±12 units or more, corresponding to a change in true left ventricular ejection fraction of ≥ 3·6 SD. In other words, when the true left ventricular ejection fraction changes by 12 units after four weeks, there is a 95% chance of detecting a change in measured left ventricular ejection fraction of ⩾ 7 units.

When the same camera position was used for repeat measurements the variability in measured left ventricular ejection fraction was reduced by <0·5 units. With observers of medium experience variability was reduced if the same person repeated the measurement but this had little effect on the variability of measurements obtained by experienced observers (table 2).

When we used the equilibrium method variability increased with time (fig 4); this is tantamount to a decrease in the ability to detect changes in left ventricular ejection fraction (table 2). The generally higher variabilities of the first pass technique that were attributable to acquisition, observer analysis, and residual errors obscured this tendency. We calculated an average value for the total variability of the first pass technique when measurements were repeated at different intervals, and we found that the average detection limits for a change in measured left ventricular ejection fraction was somewhat higher than that for comparable values with equilibrium imaging (table 2).

Our analysis was comprehensive, but not ideal statistically. It might have been improved if we had investigated some groups several times to test the sample distribution, if the data had been transformed, and if the uncertainties in estimation of the components of variance had been examined in more detail. But such procedures are often impracticable, especially when data comes from patients.

CLINICAL IMPLICATIONS

The variance component method estimates the relative impact of the many different sources of error and provides a measure of the confidence that can be put in observations. For example, cineventriculography or echocardiography in a patient with a true left ventricular ejection fraction of 0·35—that is methods that may both have a single measurement confidence interval of ±15 ejection fraction units—may give a value from 0·20 to 0·50. When a value lies at the extremes, the patient's global left ventricular function could be mistakenly regarded as being either severely reduced or almost normal. The radionuclide technique would give an equilibrium value of from 0·32 to 0·38 and a first pass left ventricular ejection fraction of between 0·29 and 0·41 (table 1)—that is values close enough to the true value to prevent the functional state being put in a wrong part of the scale.

When changes in left ventricular ejection fraction are measured the need for a method with low variability is even greater. All sources of variability contribute not once, as in single measurements, but twice because the measurement is repeated, and the detection limits are not 1·96 times the composite SD but 3·60 times SD. The consequences of this are different in the clinical situation and in the scientific setting. In scientific studies a statistically significant change in left ventricular ejection fraction may be detected in a group of patients if there is a change in the same direction in a sufficiently large proportion of patients. For the clinician, however, the question is whether a measured change in left ventricular ejection fraction in an individual patient is caused by method variability or whether it reflects a real change in true left ventricular ejection fraction. If the precision of the method is not good the true answer will not emerge and the clinician will have to rely on physical signs, which, although accepted and important, are insensitive, non-specific, and not very reproducible.[30–32]

The evaluation of methods of measurement is lagging well behind their clinical application. Many published papers do not mention method variability. Clinicians should choose their methods of measurement after a critical appraisal of all the techniques available and not merely use the most popular or well established one.

A detailed description of the statistical model and its application to the present material can be obtained from P F H–C. This work was supported in part by the Danish Heart Foundation.

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Raised concentrations of glucose and adrenaline and increased in vivo platelet activation after myocardial infarction

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SUMMARY Plasma concentration of β thromboglobulin was used as an index of in vivo platelet activation in 36 patients after acute myocardial infarction. Twelve patients had diabetes, seven had pulmonary oedema or cardiogenic shock (pump failure) or both, and 17 had uncomplicated infarcts. On the first day of admission, concentrations of β thromboglobulin were higher in the patients with diabetes and those with pump failure than in those with uncomplicated infarcts. Concentrations of β thromboglobulin in the non-diabetic patients were studied by multiple regression analysis and were significantly associated with plasma concentrations of adrenaline, pump failure, and glucose but not with noradrenaline or infarct size. When all subjects were considered together, glucose, adrenaline, and pump failure were associated with the β thromboglobulin concentration but diabetes was without significant effect.

Hyperglycaemia and raised plasma adrenaline concentration after myocardial infarction may activate platelets, and this could contribute to poor outcome in such patients.

Case fatality rates are higher in diabetic patients admitted to hospital with acute myocardial infarction than in non-diabetic patients, with the principal causes of death being refractory heart failure or cardiogenic shock (pump failure) or both.[1 2] The excess risk of pump failure in diabetic subjects does not result from more extensive necrosis,[2-5] nor is there evidence that more widespread atheroma restricts the perfusion of non-infarcted myocardium in these patients.[6] The role of hyperglycaemia remains controversial.[7-11]

The primary cause of myocardial infarction is thrombosis of a coronary vessel and the fate of this thrombus is an important determinant of outcome after myocardial infarction.[12] Reperfusion of the infarcted myocardium preserves myocardial function and improves prognosis[13 14] although the levels of enzyme release are no less.[14] The process of recanalisation may result from fibrinolysis, and diminished thrombolytic activity is associated with several risk factors for poor outcome after myocardial infarction.[15] There may be a dynamic equilibrium, however, between fibrinolysis, with consequent reperfusion, and continuing platelet aggregation and thrombosis,[16] so that haemostatic variables may also influence the possibility of recanalisation.[17]

In patients with diabetes mellitus there is a hypercoagulable state with enhanced platelet activation and increased thrombogenesis.[18] We have tested the hypothesis that in vivo platelet activation is increased both in diabetic patients and those with pump failure after acute myocardial infarction. We have also explored the relation between indices of platelet activation and metabolic and hormonal variables in such patients.

Patients and methods

We studied 36 patients admitted to hospital with acute myocardial infarction confirmed according to World Health Organisation criteria[19]: 12 consecutive

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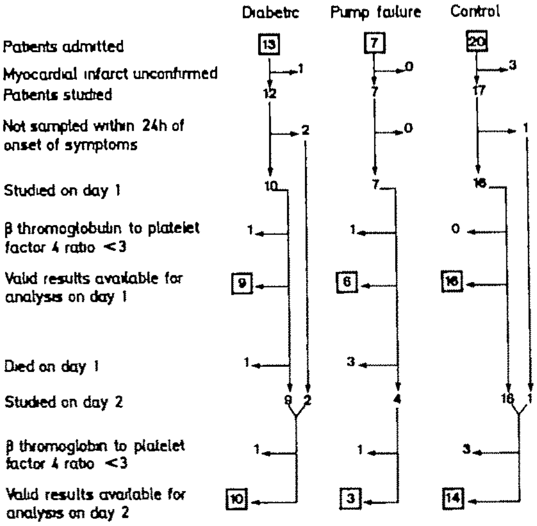
Diabetic
Pump failure
Control
Patients admitted
13
7
20
Myocardial infarct unconfirmed
1
0
3
Patients studied
12
7
17
Not sampled within 24h of onset of symptoms
2
0
1
Studied on day 1
10
7
16
β thromoglobulin to platelet factor 4 ratio <3
1
1
0
Valid results available for analyses on day 1
9
6
16
Died on day 1
1
3
Studied on day 2
8
2
4
16
1
β thromoglobin to platelet factor 4 ratio <3
1
1
3
Valid results available for analyses on day 2
10
3
14

Fig 1 *Patient numbers and design of study.*

patients with known diabetes, one with pump failure; seven consecutive patients without known diabetes in whom pump failure developed; and 17 non-diabetic patients with uncomplicated infarcts. Pump failure was defined as a sustained systolic blood pressure of < 90 mm Hg, associated with oliguria and signs of peripheral circulatory failure, with or without clinical or radiological evidence of pulmonary oedema. This classification corresponds to Killip grades C and D.[20] For each patient with diabetes or pump failure that we studied, we also studied the next patient admitted without known diabetes with apparently uncomplicated myocardial infarction as a control. The results from three other non-diabetic patients, who were studied as controls, and one diabetic patient, were not analysed because clear evidence confirming myocardial infarction did not develop (fig 1). All patients who had taken drugs known to affect platelet function, including those on calcium channel blockers, were excluded from the study.

In all patients without known diabetes glycosylated haemoglobin (HbA_{1c}) was measured on admission; none had concentrations of HbA_{1c} indicative of undiagnosed diabetes.[21] Infarct size was assessed by cumulative release of creatine kinase MB isoenzyme measured eight hourly for 48 hours[22 23] and daily measurement of peak aspartate transaminase for 48 hours from onset of symptoms. We have previously reported a reasonable correlation between these two measures of infarct size ($r = 0{\cdot}67$, $n = 28$, $p < 0{\cdot}001$[23]).

Blood samples were taken after adequate analgesia to measure catecholamines, the platelet specific proteins β thromboglobulin and platelet factor 4, plasma glucose, and HbA_{1c} shortly after admission to the coronary care unit and again on the second day of hospital admission. There was no significant difference in timing of the samples from the onset of symptoms between any of the three groups ($p > 0\ 3$, table 2). Blood was sampled from an antecubital vein through a 19 G needle without venous stasis.[24] We took care to avoid aggregation of platelets in vitro and consequent spurious rises in concentration of β thromboglobulin.[25] We used commercial kits for radioimmunoassay of β thromboglobulin (Amersham International) and platelet factor 4 (Abbott Laboratories). The within and between assay coefficients of variation for the β thromboglobulin assay were 6·9% and 10·4% and for platelet factor 4 they were 7·7% and 6·3% respectively. Samples with β thromboglobulin to platelet factor 4 ratios of less than 3:1 were excluded from analysis because such ratios reliably indicate in vitro platelet activation.[26]

Blood for catecholamine assay was taken into cooled lithium heparin tubes and stored in an ice-water slurry before centrifugation at 4° C at 1500 *g* for five minutes. Plasma was stored at −20° C until assay for plasma adrenaline and plasma noradrenaline by high performance liquid chromatography with electrochemical detection, as previously described.[27] The upper limits of normal by this method are 1·2 nmol/l for adrenaline and 2·6 nmol/l for noradrenaline and the within assay coefficients of variation are 10% and 6% respectively. Glycosylated haemoglobin was measured by isoelectric focusing with within and between assay coefficients of variation of 4·9% and 5·3%. Plasma glucose was assayed by an automated glucose oxidase method. Aspartate transaminase was measured by a spectrophotometric method (AST-optimised, BCL, Lewes, Sussex) and creatine kinase MB isoenzyme by an immunological method (BCL). Figure 1 and table 1 show the number of subjects for whom each assay was satisfactory. Catecholamine concentrations were not known in two controls.

STATISTICAL ANALYSIS

Statistical analysis was performed by Student's *t* test and least squares regression analysis, on logarithmically transformed data if appropriate. Because the subgroups were small, these regression analyses were also repeated without the observation demonstrating the largest influence on the regression coefficient (Cook's distance), to exclude the possibility that the results were dependent on a single observation. Data are presented as the mean (SD) for symmetrically distributed data and as median and range for skewed data. Multiple linear regression analysis was applied to the pooled data for all the patients and to that of the non-diabetic patients alone, with logarithmic trans-

Table 1 *Data for patients for whom valid results were available on day 1*

Group	*Age*	*Sex*	*β thromboglobulin (ng/ml)*	*Platelet factor 4 (ng/ml)*	*Glucose (mmol/l)*	*Noradrenaline (nmol/l)*	*Adrenaline (nmol/l)*	*Peak aspartate transaminase (IU/l)*	*Cumulative creatine kinase MB (IU/l)*
Diabetic:									
1	76	M	127	26	8·8	4·6	1·50	312	419
2	59	M	162	47	16·3	1·8	0·15	340	258
3	46	F	92	12	11·4	5·0	0·37	84	238
4	59	M	41	5	5·8	1·5	0·20	73	—
5	60	M	202	5	17·9	11·6	0·80	—	—
6	58	F	50	4	11·0	3·7	0·24	308	266
7	73	F	59	8·5	8·8	1·7	0·80	62	186
8	58	M	57	5·5	11·6	3·7	1·10	281	850
9	54	M	75	18	16·0	2·2	0·68	132	417
Pump failure:									
10	69	F	128	28	9·6	7·5	3·70	880	1096
11	72	F	184	7	14·6	20·7	7·30	410	1018
12	53	M	193	27	19·7	10·6	6·23	—	—
13	70	M	93	12	10·6	1·2	0·63	273	856
14	80	F	91	23	11·8	17·4	2·04	210	497
15	64	F	186	15	12·8	12·7	14·6	588	1542
Control:									
16	60	M	79	7·5	9·1	10·3	3·10	558	540
17	57	M	32	6	7·7	6·8	6·00	229	640
18	59	M	41	5	9·6	8·4	0·35	196	532
19	69	M	64	6	5·9	3·2	0·55	197	326
20	48	M	44	<1	7·2	2·8	0·36	291	703
21	77	M	84	16	5·6	8·2	1·60	95	—
22	54	M	38	<1	6·5	2·2	0·29	397	671
23	49	M	45	4·5	8·3	2·3	0·70	400	821
24	72	M	46	8·5	10·4	6·2	2·10	324	739
25	58	M	33	4·5	7·8	3·2	0·70	223	535
26	52	M	62	10	10·5	3·9	0·63	580	851
27	66	F	36	4	7·8	3·1	0·36	190	508
28	63	F	48	14·5	11·3	10·2	0·89	630	573
29	77	F	36	<1	5·7	10·2	0·40	119	161
30	53	F	30	3·5	6·5	—	—	386	—
31	59	M	49	11·9	9·0	—	—	540	—

formation as appropriate. We used the regression function of the SPSS-X program for the analysis, and we used dummy variables to explore group differences in slope and intercept. Alternative models were tested by use of sequential forced entry of the variables being tested, and the significance of F-change at each step is reported; however, the relations being tested by these models are not the only plausible explanation for the results. The appropriate F values are given for these analyses and the slopes of the fitted regression lines in the final model are presented with 95% confidence intervals. Probability values of $p < 0.05$ were regarded as statistically significant.

Power of the study

The numbers studied were adequate to demonstrate a 36% increase in plasma concentrations of β thromboglobulin in diabetic patients and a 40% increase in pump failure patients at the 5% level with a power of 0·8. The total numbers of subjects studied were sufficient to permit the detection of significant effects of individual variables on plasma concentrations of β thromboglobulin at the 5% level with a correlation coefficient of 0·36, implying that the variable determines 13% of the variance of β thromboglobulin. The regression analyses assume linearity, but there is a possibility that some significant effects may be a result of a non-linear relation. Non-significant results, in samples of this size, particularly in subgroups, are not proof of non-association.

Results

INFARCT SIZE

We studied 36 patients with confirmed myocardial infarction (fig 1). One patient with diabetes and three without died after the development of pump failure. In addition, two with diabetes and two without diabetes and with apparent uncomplicated myocardial infarction developed serious dysrhythmias (complete heart block in three of the patients and one episode of ventricular fibrillation in a diabetic patient). There were no deaths from these complications. Table 1 shows data on all patients. There was no significant difference in ages between the groups ($p > 0.2$). Median peak serum concentration of aspartate transaminase and cumulative release of creatine kinase MB were significantly greater in the controls than in the diabetics (table 2). Infarct size

Table 2 *Details of age, infarct size, and plasma β thromboglobulin concentrations in patients studied. Numbers are shown in parentheses*

				Significance (Student's t test)		
	Diabetic	*Pump failure*	*Control*	*Diabetic v control*	*Pump failure v control*	*Diabetic v pump failure*
Age (mean (SD))	60 (9)	68 (9)	61 (9)	NS	NS	NS
Peak aspartate transaminase (IU/l) (median and range)	167 (84–340) (11)	410 (210–880) (5)	291 (95–630) (17)	<0·05	NS	<0·05
Creatine kinase MB isoenzyme cumulative release (IU/l) (median and range)	266 (186–850) (9)	1017 (497–1542) (5)	640 (161–851) (15)	<0·02	<0·05	<0·005
Day 1						
Blood urea (mmol/l) (mean (SD))	6·9 (1·8) (8)	13·3 (5·1) (6)	6·6 (2·8) (16)	NS	<0·005	<0·01
Admission plasma glucose (mmol/l) (mean (SD))	11·96 (4·03) (9)	13·18 (3·63) (6)	8·06 (1·80) (16)	<0·005	<0·001	NS
Adrenaline (nmol/l) (median and range)	0·68 (0·15–1·50) (9)	5·0 (0·63–14·6) (6)	0·7 (0·29–6·0) (16)	NS	<0·005	<0·001
Noradrenaline (nmol/l) (median and range)	3·7 (1·5–11·6) (9)	11·7 (1·2–20·7) (6)	5·1 (2·2–10·3) (16)	NS	NS	<0·05
β thromboglobulin (ng/ml) (median and range)	67 (41–162) (8)*	156 (91–193) (6)	45 (33–84) (16)	<0·002	<0·001	NS
Platelet factor 4 (ng/ml) (median and range)	10 (4–47) (8)*	19 (7–28) (6)	5·5 (<1–16) (16)	NS	<0·02	NS
Time from onset of symptoms (h) (median and range)	12 (8–21)	12 (5–24)	15 (4–22)	NS	NS	NS
Day 2:						
β thromboglobulin (ng/ml) (median and range)	45 (30–126) (10)	148 (138–167) (3)	42 (22–69) (14)	NS	<0·001	<0·01

*Value in diabetic patient with pump failure is excluded.

estimated by cumulative creatine kinase MB release was greater in the patients with pump failure than in the controls.

PLASMA CONCENTRATIONS OF β THROMBOGLOBULIN

In seven samples (2 on day 1 and 5 on day 2) the ratio of β thromboglobulin to platelet factor 4 was <3, indicating possible in vitro platelet activation (fig 1). Plasma β thromboglobulin was highest (202 ng/ml) in the diabetic patient with pump failure. This result was excluded from the statistical comparisons of diabetic and non-diabetic patients. The median β thromboglobulin concentration on day 1 in the non-diabetic patients with pump failure was significantly greater than that in the control group of non-diabetic patients with uncomplicated myocardial infarction. The median β thromboglobulin concentration was also significantly greater in the diabetic patients than in the control group. Although the concentration of blood urea was significantly higher in the patients with pump failure, there was no relation between blood urea and β thromboglobulin concentration in any group ($r = -0{\cdot}32$ to $0{\cdot}20$, $p > 0{\cdot}2$). In the controls there was a weak relation between age and β thromboglobulin concentration ($r = 0{\cdot}28$; $p > 0{\cdot}2$) and the mean age difference of seven years between the controls and pump failure group might explain a difference of only 3·1 ng/ml in β thromboglobulin concentrations between the groups. On the second day after the onset of symptoms, the median β thromboglobulin concentration in diabetic patients was no longer significantly different from that in controls ($p > 0{\cdot}1$). The median β thromboglobulin concentration in patients with pump failure remained high; however, three of the seven patients with pump failure had died before resampling (fig 1).

DETERMINANTS OF β THROMBOGLOBULIN CONCENTRATIONS IN NON-DIABETIC PATIENTS WITH OR WITHOUT PUMP FAILURE

Concentrations of glucose, adrenaline, and noradrenaline and cumulative creatine kinase MB release were significantly higher in patients with pump failure than in controls (table 2) (figs 2a and 3a). In the non-diabetic patients as a whole there were significant correlations between concentrations of β thromboglobulin and adrenaline ($r = 0{\cdot}71$, $p < 0{\cdot}0002$), glucose ($r = 0{\cdot}73$, $p < 0{\cdot}0001$), cumulative creatine kinase MB release ($r = 0{\cdot}57$, $p < 0{\cdot}01$), and noradrenaline ($r = 0{\cdot}47$, $p < 0{\cdot}02$). All of these correlation coefficients were increased when the relations were reanalysed after omitting the observation with the largest Cook's distance ($r = 0{\cdot}84$, 0·78, 0·80, and 0·59 respectively). Because there are significant interrelations between these variables[22] we used multiple regression analysis to test the hypothesis that adrenaline and glucose concentrations determine the concentrations of β thromboglobulin

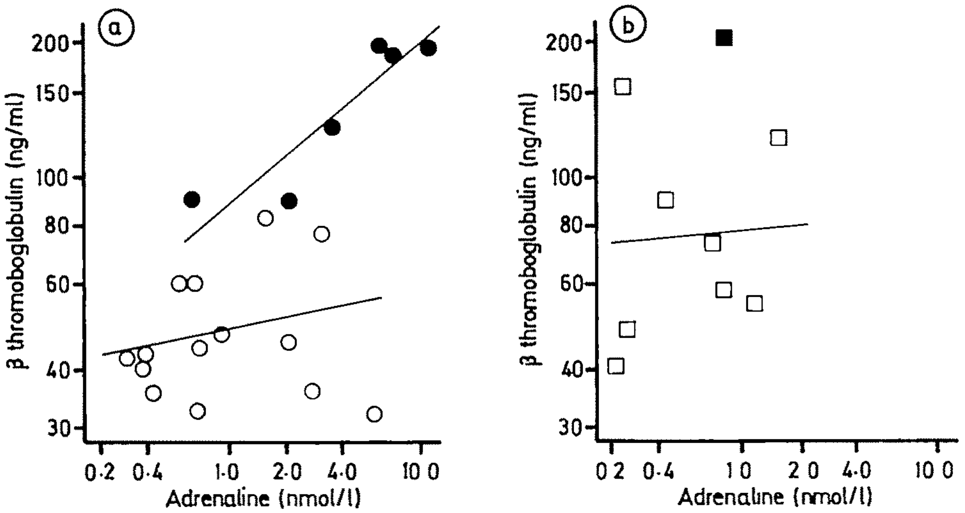

Fig 2 *The relation between plasma concentrations of β thromboglobulin and adrenaline in (a) non-diabetic and (b) diabetic patients after acute myocardial infarction.* ●*, non-diabetic patients with pump failure;* ○*, non-diabetic controls;* ■*, diabetic with pump failure;* □*, diabetics without pump failure. Correlation coefficients (r) are: non-diabetic patients with pump failure, 0·88 (p < 0·01); non-diabetic controls, 0·26 (p = 0·19); diabetic patients without pump failure, 0·04 (p > 0·4).*

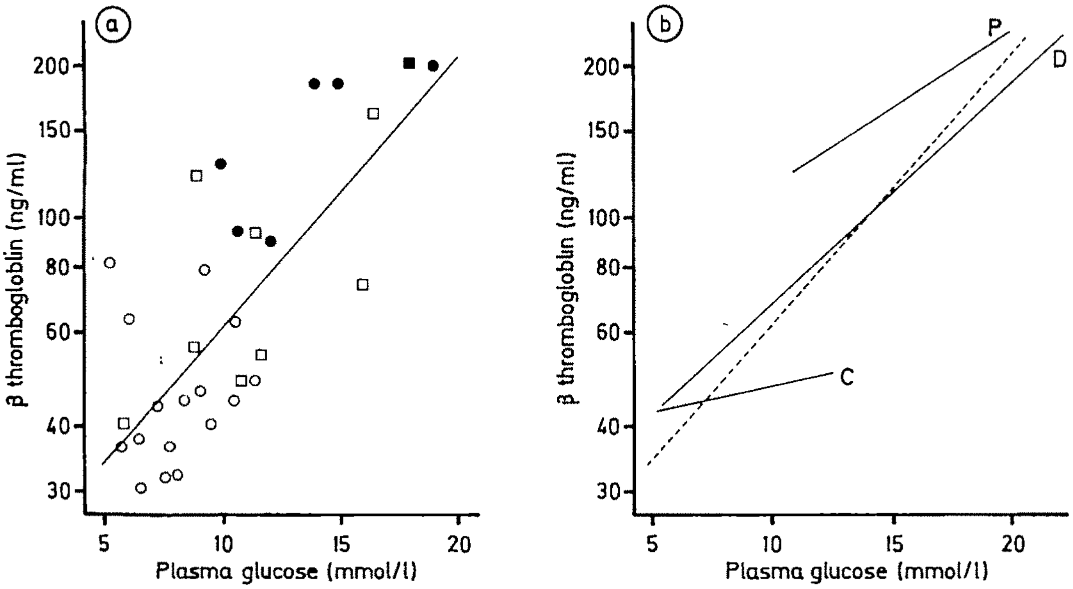

Fig 3 *(a) The relation between plasma concentrations of β thromboglobulin and glucose in patients after acute myocardial infarction* ●*, non-diabetic patients with pump failure,* ○*, non-diabetic controls,* ■*, diabetic with pump failure;* □*, diabetics without pump failure. (b) Regression lines for plasma concentrations of β thromboglobulin and glucose in all subjects (dotted line)—slope = 0·119 (95%CI 0·077 to 0·161); in non-diabetic patients with pump failure (P)—slope = 0·066 (95%CI −0·032 to 0·164); in non-diabetic controls (C)—slope = 0·020 (95%CI −0·079 to 0·119); in diabetic patients without pump failure (D)—slope = 0·072 (95%CI −0·038 to 0·182)*

Table 3 *Multiple regression analysis for determinants of β thromboglobulin levels on day 1 after admission with myocardial infarction (a) in non-diabetic patients and (b) in all subjects combined*

(a) Non-diabetics

Variable(s) in model	*Variable added*	*F (degrees of freedom)*	*Multiple r^2*	*Significance*
	Adrenaline	19·01 (1,18)	0·51	<0·0005
Adrenaline	Glucose	5·87 (1,17)	0·64	0·028
Adrenaline, glucose	Pump failure (intercept)	12·18 (1,16)	0·79	<0·005

Final model

Variable	*Slope of fitted regression line*	*95% confidence interval*	*Significance*
Adrenaline	0·138	−0·022, 0·298	0·087
Glucose	0·024	−0·039, 0·087	0·429
Pump failure (intercept)	0·750	0·294, 1·205	0·003

(b) All cases

Variable(s) in model	*Variable added*	*F (degrees of freedom)*	*Multiple r^2*	*Significance*
	Glucose	33·60 (1,29)	0·54	<0·0001
	Adrenaline	7·34 (1,27)	0·21	0·012
Glucose	Adrenaline	4·78 (1,26)	0·59	0·038
Adrenaline	Glucose	24·20 (1,26)	0·59	<0·0005
Glucose, adrenaline	Diabetes (intercept)	1·39 (1,25)	0·61	0·249
Glucose, adrenaline, diabetes	Pump failure (intercept)	10·17 (1,24)	0·73	0·004

Final model

Variable	*Slope of fitted regression line*	*95% confidence interval*	*Significance*
Adrenaline	0·104	−0·039, 0·249	0·15
Glucose	0·049	0·001, 0·098	0·047
Pump failure (intercept)	0·662	0·234, 1·091	0·004
Diabetes (intercept)	0·362	0·017, 0·707	0·040

in these subjects. Adrenaline was the major catecholamine determinant of plasma concentrations of β thromboglobulin (table 3a), with plasma glucose as an additional factor. In this model, pump failure still provided an additional significant contribution, but infarct size, estimated by cumulative creatine kinase MB isoenzyme release, and noradrenaline provided no additional contribution. In the final model, however, only pump failure remained as a significant variable.

DETERMINANTS OF β THROMBOGLOBULIN LEVELS IN NON-DIABETIC AND DIABETIC PATIENTS (TABLE 3B)

We also used multiple regression analysis to test the hypothesis that concentrations of glucose and adrenaline determine the raised plasma concentrations of β thromboglobulin in all the patients we studied. Glucose and adrenaline were both significant determinants of β thromboglobulin in this model, and each retained a significant effect in the presence of the other variable. When glucose was included in the analysis, forced entry of diabetes did not contribute significantly to β thromboglobulin. The entry of pump failure to the analysis, however, made a significant additional contribution as a determinant of plasma β thromboglobulin, even when glucose and adrenaline were included in the analysis. Infarct size, glycosylated haemoglobin A_{1c}, and noradrenaline were without significant effect. In the final model, glucose, pump failure, and diabetes were the only significant independent variables.

Figure 3 shows the relation between simultaneous concentrations of plasma glucose and β thromboglobulin in diabetic and non-diabetic patients with and without pump failure. There is a significant relation between the concentrations of blood glucose and β thromboglobulin in all subjects (r = 0·73, p < 0·001). The regression lines for all three groups did not have significantly different slopes, although multiple regression analysis showed that the intercept for subjects with pump failure was significantly higher than that for other subjects (F = 11·88, 27 df, p < 0·002). Reanalysis of the regression line without the observation showing the largest Cook's distance improved the relation (r = 0·77, p < 0·001) without markedly affecting the slope (0·128, 95% confidence interval 0·087 to 0·169).

Discussion

There are several difficulties in interpreting studies of platelet aggregation in patients with myocardial infarction. In vitro tests of platelet function may not represent the situation in vivo, both because of artefacts implicit in the preparation of platelet rich plasma,[28] and because metabolic changes in other blood components may also influence platelet aggregation.[29] Some studies of platelet aggregation after myocardial infarction have demonstrated platelet hypoaggregability,[30 31] which may result either from dissociation of circulating platelet aggregates during preparation of platelet rich plasma, or from in vivo consumption of the more active platelets. Because in vitro studies of platelet aggregation may not reflect the in vivo situation, circulating concentrations of α granule proteins have been used to indicate in vivo platelet activation. The likelihood of in vitro release of β thromboglobulin is increased on admission after myocardial infarction[32] which means that such studies must be careful to exclude data in which there is evidence of in vitro platelet activation.[26] Previous studies of plasma concentrations of β thromboglobulin after acute myocardial infarction have generally demonstrated an increase,[32-42] which in one study was more pronounced in patients with left ventricular failure or cardiogenic shock,[41] but the data have never been analysed after exclusion of subjects with evidence of in vitro activation. It is likely that in future the reference standard for evidence of in vivo platelet activation will be the concentration of the urinary thromboxane metabolite, 2,3-dinor-thromboxane B_2.[43 44] In one recent study in 14 patients, this did not correlate with infarct size.[43]

We have demonstrated significant differences in plasma concentrations of β thromboglobulin between diabetic and non-diabetic patients in the first 24 hours after infarction. Moreover, plasma concentrations of β thromboglobulin were different in patients with uncomplicated myocardial infarction and those with pump failure. Although this study cannot establish whether this was a cause or an effect, the fall in concentrations of β thromboglobulin by the second day in diabetic patients suggests that the rise was secondary to the infarction. A recent report, which showed that radiolabelled platelets are incorporated into thrombus after myocardial infarction, has suggested that such a process may be responsible for thrombus proliferation and infarct extension.[16] It is also possible that excess platelet activation might prevent recanalisation of a thrombosed vessel.

We studied the determinants of plasma concentrations of β thromboglobulin by multiple regression techniques. Using forced entry of different variables, we tested the hypothesis that concentrations of adrenaline and glucose were largely responsible for the variance of β thromboglobulin concentrations in patients in different subgroups. Nevertheless, we recognise that this cannot provide proof of causation, and that other models are also compatible with the observed relation.

In the non-diabetic patients concentrations of β thromboglobulin were highest in those with pump failure who sustained more extensive infarction and in whom adrenaline concentrations were high. Platelets have α adrenergic receptors and catecholamines can induce aggregation either directly or by increasing sensitivity to other agonists. Adrenaline has a more powerful effect than noradrenaline.[45-47] The number of these α receptors may be reduced immediately after myocardial infarction, perhaps as a response to the raised concentrations of catecholamines found then.[48] We have previously described a relation between plasma concentrations of adrenaline early in the course of infarction and the size of the myocardial infarction determined by enzyme release.[23] In non-diabetic patients in whom pump failure develops, it is possible that extensive initial thrombosis is associated with high adrenaline concentrations which enhance platelet activation and thrombogenesis, thereby restricting reperfusion; the envisaged vicious circle might then only be broken by blocking adrenergic stimulation or platelet activation. A combination of pharmacological thrombolysis[49 50] with blockade of platelet aggregation might therefore be a logical approach to the treatment in patients after myocardial infarction. This is currently being tested in the ISIS-2 trial. Our results do suggest, however, that the increase in platelet activation found in patients with pump failure cannot be totally explained on the basis of raised concentrations of adrenaline.

In diabetic patients platelet activation was increased after myocardial infarction even in the absence of pump failure. Increased concentrations of β thromboglobulin were reported in diabetic patients with or without microangiopathy,[51-55] but similar studies have not been performed in patients after myocardial infarction. Patients with myocardial infarction in whom the occluded coronary artery does not recanalise have more residual impairment of myocardial function[12-14] but have not been shown to have larger infarcts estimated by cumulative enzyme release.[14] It is possible that the reports of a higher incidence of haemodynamic complications in diabetic patients at any given level of enzyme release[2-5] are explicable on the basis of differing patterns of reperfusion, determined both by increased platelet activation and diminished fibrinolysis.[56] Confirmation of this hypothesis depends on the patterns of coronary angiograms[12] or enzyme release.[14]

We have attempted to define the determinants of platelet activation in diabetic patients after myocardial infarction. Glucose concentrations seem to be the major determinant of platelet activation without any additional contribution from diabetes per se. As in non-diabetic patients adrenaline concentrations and the presence of pump failure both contributed significantly to the concentration of βthromboglobulin. We have shown that in the unstimulated state platelets from diabetic subjects release more noradrenaline than platelets from non-diabetic subjects,[57] a finding which may parallel the additive effects of hyperglycaemia and adrenaline concentrations on platelet activation after myocardial infarction. The platelet α receptor may have an important role generally in stress induced aggregation in diabetic subjects; enhanced platelet aggregability after hypoglycaemia may be simulated in vitro by adding similar concentrations of adrenaline, and may be blocked by α blockade.[58]

We have demonstrated that the relation between plasma concentrations of β thromboglobulin and glucose is similar in diabetic and non-diabetic patients after myocardial infarction. There are two possible explanations for these findings. Most simply, higher plasma concentrations of glucose in diabetic patients after myocardial infarction may enhance platelet activation, in which case it might follow that tight control of blood glucose concentrations early in the course of myocardial infarction would reverse activation. The excess activation, however, may also result from an enhanced sensitivity of diabetic platelets to circulating catecholamines, which may mean that control of plasma glucose alone would not affect thrombogenesis. These hypotheses remain to be tested.

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Influence of aging on Doppler echocardiographic indices of left ventricular diastolic function

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SUMMARY The influence of age on six Doppler echocardiographic indices of left ventricular diastolic function was assessed in 86 normal volunteers aged from 20 to 74 years (mean 36). Five of the six indices showed a linear relation with age. Duration of isovolumic relaxation and maximal late diastolic (atrial) flow velocity increased significantly with age ($r = 0{\cdot}34$ and $r = 0{\cdot}69$, respectively). Conversely, maximal early diastolic flow velocity, the rate of decrease (deceleration) of flow velocity in early diastole, and the ratio between maximal early and late diastolic flow velocities decreased significantly with age ($r = -0{\cdot}30$, $r = -0{\cdot}40$, and $r = -0{\cdot}63$, respectively). Duration of the early diastolic flow velocity peak did not show a linear relation with age ($r = 0{\cdot}04$). Comparison of Doppler indices of diastolic performance among different age groups (20 to 29 years, 30 to 49 years, and 50 to 74 years) also showed an influence of aging on these diastolic variables. Isovolumic relaxation was significantly longer in older subjects than in either the intermediate or the younger age groups. In addition, both the rate of decrease of flow velocity in early diastole and the ratio between maximal early and late diastolic flow velocities were significantly reduced in older subjects. Multivariate linear regression analysis showed that after adjustment for left ventricular wall thickness and cavity dimension, percentage systolic shortening, and heart rate, age continued to correlate significantly with most Doppler indices of diastolic function.

The isovolumic relaxation phase and the early and late filling phases of diastole, as assessed by Doppler echocardiography, are importantly and independently affected by aging. Hence the effects of age should be taken into account when the normal limits for Doppler indices of left ventricular diastolic function are defined.

Recently, Doppler echocardiography has been used to assess left ventricular diastolic function in patients with various cardiac diseases and in normal subjects.[1–10] Indices of diastolic function obtained by Doppler echocardiography have also been shown to correlate well with those measured by either contrast angiography[4] or radionuclide angiography.[5 10] Some determinants of left ventricular filling assessed by Doppler, however, seem to be affected by age.[1 7 11] Such age related changes in left ventricular filling patterns may be important in defining normal values for Doppler indices of diastolic function.

To achieve a better understanding of the effects of aging on Doppler indices of left ventricular diastolic performance we obtained Doppler echocardiographic measurements of isovolumic relaxation and of the early and late filling phases of diastole in a group of healthy volunteers with a wide range of ages.

Subjects and methods

STUDY POPULATION

We measured Doppler echocardiographic indices of left ventricular diastolic function in 86 healthy volunteers (48 men and 38 women) who were aged from 20 to 74 years (mean 36). None had a clinical history of cardiac disease or of systemic hypertension and all had a normal M mode and cross sectional echocardiogram. The data were examined by linear regression analysis. In addition, we compared Doppler diastolic measurements among three age

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groups: (*a*) 35 subjects aged from 20 to 29 years (mean 22); (*b*) 33 aged 30 to 49 years (mean 40); and (*c*) 18 aged 50 to 74 years (mean 57). Doppler indices of left ventricular diastolic flow velocity in men and women (within each age group) were also compared to determine whether sex differences independently influence diastolic performance.

DOPPLER ECHOCARDIOGRAPHY

We used an Advanced Technology Laboratory Mark 500 ultrasound system for the Doppler echocardiographic studies. This instrument combines a pulsed Doppler flow analyser with a 3·0 MHz, on line, two dimensional wide angle (90°) mechanical sector scanner. The system has a movable cursor and the Doppler sample volume can be positioned anywhere in the cross sectional sector plane and at any depth up to 17 cm. The depths we used to obtain the left ventricular diastolic flow velocity profiles ranged from 9 to 13 cm. The dimensions of the sample volume at these depths were 5–7 mm (length) × 1·5 mm (diameter) × 1·5 mm (depth).

Doppler output was available as an audio signal and as a spectral display of the flow velocity profile. The spectral display was obtained by electronic fast-Fourier transform analysis of the Doppler signal, with sampling at 10 ms intervals and division of the signal into 128 frequency bins. The flow velocity profile was displayed as a waveform composed of small individual grey and black blocks that appeared simultaneously on a monitor with the lead II electrocardiogram and a phonocardiogram and was recorded on a strip-chart recorder at a paper speed of 100 mm/second. The setting of the instrument was adjusted to use the lowest possible filters.

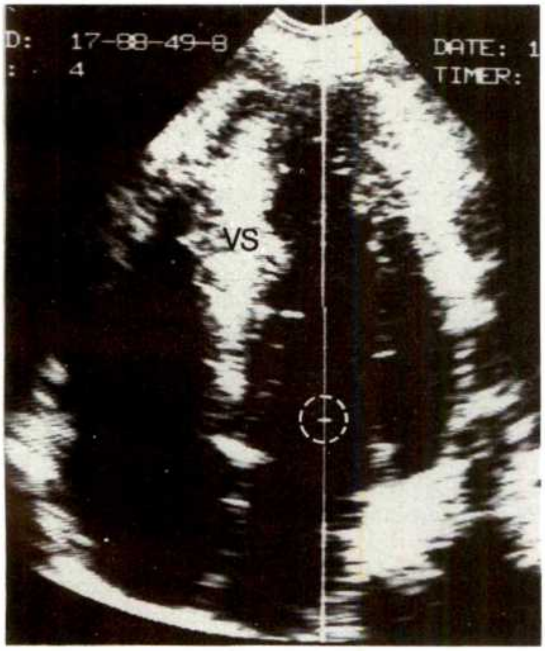

Fig 1 *Stop frame cross sectional echocardiogram showing the position of the Doppler sample volume (enclosed within the broken circle) that was used for left ventricular diastolic flow velocity waveforms. The sample volume is positioned within the inflow area of the left ventricle. VS, ventricular septum. Reproduced with permission of American College of Cardiology from Spirito et al.*[5]

The Doppler recordings were obtained during quiet respiration with the subject in a lateral recumbent position. The transducer was positioned at or slightly to the left of the cardiac apical impulse, and was oriented to obtain an apical four chamber view of the heart that gave good visualisation of the left ventricular cavity and maximal excursion of the mitral valve leaflets. The cursor line was directed through a plane traversing the left ventricle from the apex to the mitral valve annulus. The angle between the presumed direction of the diastolic blood flow and the orientation of the ultrasound beam (cursor) was estimated to be zero or < 20° in each subject. The sample volume was placed in the inflow area of the left ventricle, about 1 cm from the mitral valve annulus (fig 1), and the position of the sample along the cursor line was adjusted until the maximal diastolic flow velocities were recorded and the graphic quality of the Doppler waveform was most clearly defined.

QUANTITATIVE ASSESSMENT OF DIASTOLIC FLOW VELOCITY WAVEFORM

In each subject we chose for analysis three cardiac cycles with the most clearly defined flow velocity waveform and the steepest descent of flow velocity in early diastole. Left ventricular diastolic flow velocity waveforms from the three cardiac cycles were measured and the values were averaged for (figure 2a) (*a*) time interval from the first positive deflection of the aortic closing component of the second heart sound to the onset of the diastolic flow velocity waveform (A_2–D), a measure of the duration of isovolumic relaxation[8]; (*b*) duration of the early diastolic peak of flow velocity defined as the time interval from the onset of this peak to the time when flow velocity returned to baseline (D–F); (*c*) rate of decrease (deceleration) of flow velocity in early diastole (EF) calculated as the ratio E–E′ to E′–F; (*d*) maximal early diastolic flow velocity measured as the height of the early diastolic peak of flow velocity (E); (*e*) maximal late diastolic flow velocity (which is due to atrial contraction) measured as the height of the late diastolic peak of flow velocity (A); (*f*) the ratio

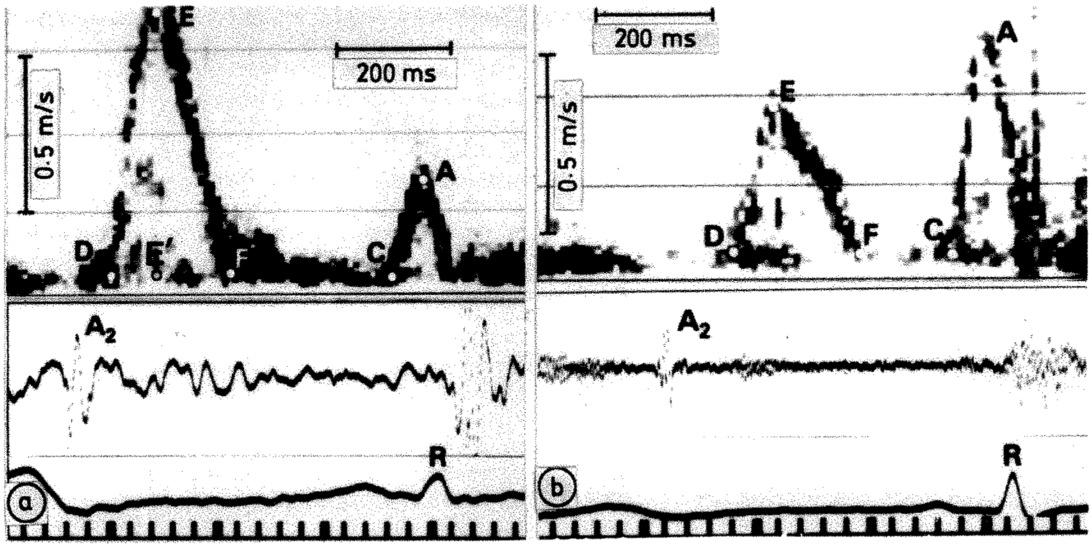

Fig 2 *Doppler left ventricular diastolic flow velocity waveforms from two normal volunteers. (a) That of the younger subject (age 23 years) shows a shorter duration of isovolumic relaxation (A_2–D) and rapid rate of decrease of flow velocity in early diastole (EF); maximal early diastolic flow velocity (E) is high relative to maximal late diastolic flow velocity (A), giving an E:A ratio of > 1. (b) The waveform in the older subject (age 58 years) shows prolonged duration of isovolumic relaxation (A_2–D) and reduced rate of decrease (descent) of flow velocity in early diastole (EF); maximal late diastolic (atrial) flow velocity (A) is increased relative to maximal early diastolic flow velocity (E), giving an E:A ratio of < 1.*

between the maximal early and late diastolic flow velocities (E:A).

Because the flow velocity waveform is displayed as a grey scale line of variable thickness, the points D, E, and A on the flow velocity contour were identified as the midpoints of the grey scale spectrum. The slope EF was defined by the construction of a straight line that passed through the midportion of the grey scale spectrum and corresponded to the descent of the early diastolic flow velocity peak. When the slope EF was curved rather than straight, EF was constructed as the line that identified the maximal incline of the slope.[5 8] Because the contour of the flow velocity waveforms often shows a wide spectral spread at the end of the early flow velocity peak (point F on fig 2a), this point was identified as the intersection between the line of the descent of the early diastolic flow velocity peak and the baseline of the peak.[5 8] At rapid heart rates (over about 90 beats/minute) the flow velocity curve does not return to baseline between the E and A peaks. In our subjects, however, the highest heart rate was 73 beats/minute; thus all flow velocity curves analysed as part of this study returned to baseline at point F.

Reproducibility of these Doppler diastolic indexes has been shown to be satisfactory with a relatively low intraobserver and interobserver variability.[5]

STATISTICAL ANALYSIS

Data were expressed as mean (2 SD). Relations between age and Doppler indices of left ventricular diastolic performance were assessed by linear regression analysis. Differences in Doppler diastolic indices between age groups were determined by the one way analysis of variance and those between sexes by the Student's unpaired *t* test. To assess whether the effect of age on Doppler indices of diastolic function is independent of the influence of other variables, we used a multivariate linear regression analysis.[12] Specifically, the influence of the following variables was assessed: ventricular septal and posterior left ventricular free wall thicknesses; left ventricular cavity dimensions at end diastole and end systole; percentage fractional shortening; and heart rate.

Results

RELATION BETWEEN AGE AND DOPPLER INDICES OF DIASTOLIC FUNCTION

Five of the six Doppler diastolic indices measured in the present study showed a linear relation with age (table 1). The duration of isovolumic relaxation and maximal late diastolic (atrial) flow velocity increased

Table 1 *Relation between Doppler indices of left ventricular diastolic function and age*

Doppler indices	*Correlation coefficient (r)*	*Statistical significance (p)*
Isovolumic relaxation	0·39	<0·001
Duration of early flow velocity peak	0·04	>0·05
Deceleration of early flow velocity	−0·40	<0·001
Early maximal flow velocity	−0·30	<0·005
Late maximal flow velocity	0·69	<0·001
Ratio of early late maximal flow velocities	−0·63	<0·001

with age (fig 3). Conversely, maximal early diastolic flow velocity, the rate of decrease (deceleration) of flow velocity in early diastole, and the ratio between the maximal early and late diastolic flow velocities decreased with age (fig 4). The duration of the early diastolic peak of flow velocity did not show a linear relation with age. Table 1 gives the values of the correlation coefficients of the regressions and their statistical significance.

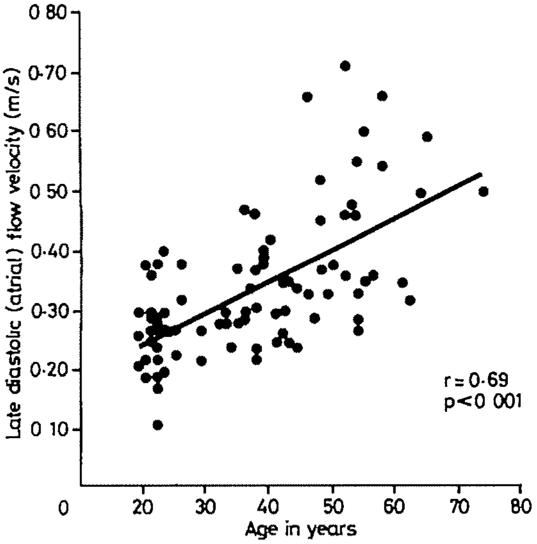

Fig 3 *Relation between age and maximal late diastolic (atrial) flow velocity (A).*

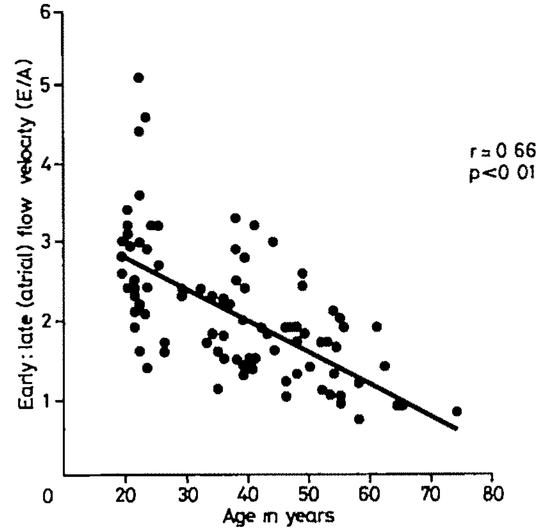

Fig 4 *Relation between age and the ratio of maximal early diastolic to late diastolic (atrial) flow velocities (E:A).*

COMPARISON OF DOPPLER DIASTOLIC INDICES IN DIFFERENT AGE GROUPS

Several Doppler indices of left ventricular diastolic performance were significantly different in the three age groups (table 2 and fig 2). Isovolumic relaxation time was longer in the older subjects (84 (12) ms) than in the younger subjects (72 (12) ms; p < 0·001), and was also longer in the intermediate (80 (12) ms) age group than the younger age group (p < 0·01) (fig 5). Furthermore, the rate of decrease (deceleration) of flow velocity in early diastole was lower in the older subjects (4·2 (1·2) m/s^2) than in the younger subjects (5·5 (1·2) m/s^2; p < 0·001), and it was also lower in the intermediate (4·7 (1·1) m/s^2) age group than the younger age group (p < 0·01) (fig 6). The ratio between the maximal early and late diastolic flow velocities was also lower in the older subjects (1·2 (0·4) than in either the intermediate (2·0 (0·6); p < 0·002) or the younger subjects (2·7 (0·7); p < 0·001) (fig 7). A ratio of < 1 was identified in five (28%) of the 18 subjects who were 50 years of age or older, whereas this ratio was > 1 in each of the 68 study

Table 2 *Comparison of Doppler indices of diastolic function in three age groups*

Age (yr)	*Isovolumic relaxation (ms)*	*Duration of early flow velocity peak (ms)*	*Deceleration of early flow velocity (m/s^2)*	*Early maximal flow velocity (m/s)*	*Late maximal flow velocity (m/s)*	*Early late maximal flow velocities*
20–29	72 (12)	218 (30)	5·5 (1·2)	0·69 (0·12)	0·27 (0·07)	2·7 (0·7)
30–49	80 (12)*	220 (27)	4·7 (1·1)*	0·62 (0·14)	0·33 (0·07)	2·0 (0·6)†
50–74	84 (12)†	221 (33)	4·2 (1·2)†	0·59 (0·14)	0·46 (0·13)	1·2 (0·4)†‡

*p < 0·01 compared with 20–29 year old subjects, †p < 0·001 compared with 20–29 year old subjects, ‡ p < 0·002 compared with 30–49 year old subjects

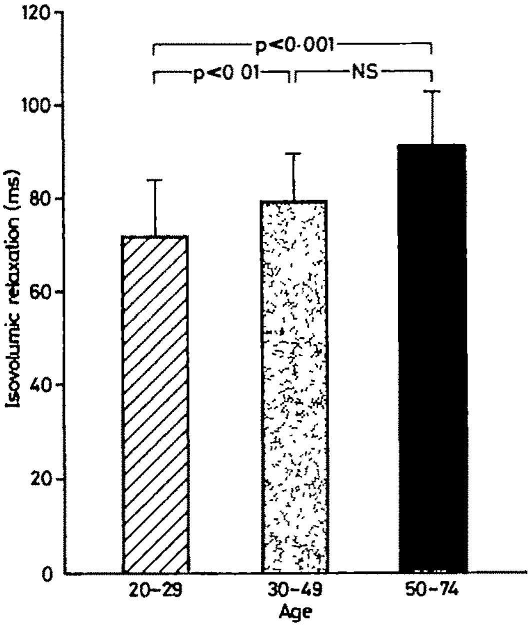

Fig 5 *Comparison of duration of isovolumic relaxation (A_2–D) in three age groups.*

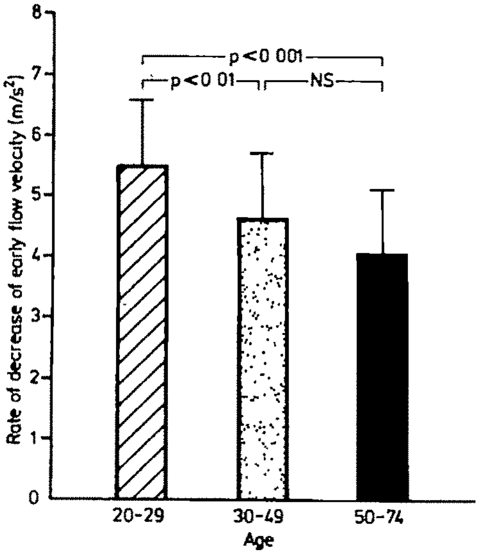

Fig 6 *Comparison of the rate of decrease (deceleration) of flow velocity in early diastole (EF) in three age groups.*

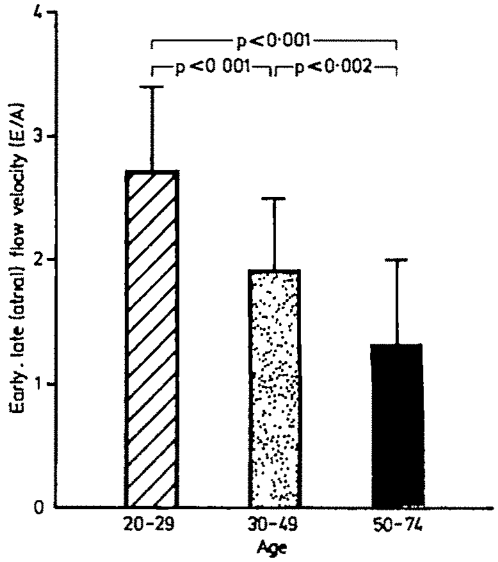

Fig 7 *Comparison of the ratio between the maximal early and late diastolic (atrial) flow velocities (E:A) in three age groups.*

subjects who were younger than 50 ($p < 0\ 001$). Heart rate was lower in the younger individuals (56 (7) beats/minute) than in the older ones (61 (6) beats/minute; $p < 0{\cdot}02$). In the intermediate age group the heart rate (59 (6) beats/minute) was not significantly different from that of the other two groups.

No differences were identified between the sexes for Doppler diastolic indices, except for a shorter duration of the early flow velocity peak in women aged 20–29 (table 3).

MULTIVARIATE ANALYSIS

Multivariate linear regression analysis showed that age is an independent, strong determinant of most Doppler indices of left ventricular diastolic flow velocity. A significant correlation persisted between age and the duration of isovolumic relaxation, rate of decrease of flow velocity in early diastole, maximal late diastolic flow velocity, and the ratio between maximal early and late diastolic flow velocities after adjustment for left ventricular dimensions, percentage fractional shortening, and heart rate (table 4). Hence, as shown in table 4, these multivariate regression coefficients and the associated p values did not differ from those of the univariate analysis. After adjustment for these independent variables, however, age no longer correlated significantly with maximal early diastolic flow velocity.

Table 3 *Comparison of Doppler indices of diastolic function in men and women*

Group	*Isovolumic relaxation (ms)*	*Duration of early flow velocity peak (ms)*	*Deceleration of early flow velocity (m/s²)*	*Early maximal flow velocity (m/s)*	*Late maximal flow velocity (m/s)*	*Early:late maximal flow velocities*
Age 20–29						
Men	71 (10)	226 (30)*	5·4 (1·2)	0·70 (0·10)	0·26 (0·06)	2·8 (0·8)
Women	74 (12)	203 (22)*	5·7 (1·2)	0·66 (0·12)	0·28 (0·07)	2·6 (0·9)
Age 30–49:						
Men	82 (11)	224 (23)	4·6 (1·2)	0·59 (0·14)	0·35 (0·09)	1·8 (0·6)
Women	79 (11)	217 (31)	4·8 (1·4)	0·64 (0·13)	0·32 (0·05)	2·0 (0·5)
Age 50–74:						
Men	84 (9)	217 (36)	4·2 (1·1)	0·55 (0·14)	0·50 (0·15)	1·1 (0·2)
Women	84 (19)	224 (32)	4·2 (0·8)	0·61 (0·15)	0·49 (0·12)	1·3 (0·5)

*p < 0·025; no other comparisons in the table were statistically significant.

Table 4 *Regression analyses of the relation between Doppler indices and age*

	*Univariate analysis**			*Multivariate analysis†*		
Doppler indices	*b*	*SE*	*p*	*b*	*SE*	*p*
Isovolumic relaxation	0·35	0·09	<0·001	0·34	0·11	<0·01
Duration early flow velocity peak	0·08	0·23	>0·05	0·35	0·26	>0·05
Deceleration early flow velocity	−0·04	0·01	<0·0001	−0·04	0·01	<0·001
Early maximal flow velocity	−0·003	0·001	<0·005	−0·002	0·001	>0·05
Late maximal flow velocity	0·006	0·001	<0·0001	0·005	0·0007	<0·0001
Early late maximal flow velocities	−0·04	0·005	<0·0001	−0·03	0·006	<0·0001

*From the regression analysis to measure the effect of age on each of the dependent Doppler indices of diastolic function.
†From the multivariate linear regression analysis to measure the effect of the set of independent variables (age, ventricular septal and posterior free wall thickness, left ventricular cavity dimensions, percentage fractional shortening, and heart rate) on each of the dependent Doppler indices of diastolic function.
b, regression coefficient for age.

Discussion

The effects of aging on left ventricular diastolic performance have not been studied extensively in human beings, in part because it is difficult to obtain data from large numbers of healthy individuals by invasive techniques such as cardiac catheterisation. Nevertheless, haemodynamic data obtained in small numbers of people without heart disease have suggested that the normal left ventricle becomes stiffer and diastolic filling is altered with aging.[13] Additional information on the influence of aging on diastolic performance has come from indirect, non-invasive measurements. Observations obtained from the mitral valve echogram have suggested that the rate of early left ventricular filling is reduced in healthy elderly people.[14-17] More recently, data obtained from the Doppler diastolic flow velocity waveform also seem to indicate that the filling patterns of the left ventricle may be influenced by aging.[1,7] In particular, the relative contribution of atrial systole to overall left ventricular filling seems to increase with age.[1,7] In addition, a recent investigation by radionuclide angiography has shown a strong relation between age and peak filling rate.[18]

The findings of the present investigation of a large population of healthy volunteers confirm and extend these previous observations. In our study, age related changes were identified for five of the six of the Doppler indices of diastolic performance that were analysed. These alterations affected the isovolumic phase as well as the early and late filling phases of diastole. Aging was associated with an increased duration of isovolumic relaxation and a reduced rate of decrease of flow velocity in early diastole. In addition, maximal early diastolic flow velocity decreased and late diastolic flow velocity (largely owing to atrial systole) increased linearly with age; hence, the ratio between early and late diastolic flow velocity was significantly lower in older subjects. The enhanced flow velocity during atrial systole probably represents a compensatory mechanism for the reduced flow velocity during the early phase of diastole.

Alterations in the Doppler left ventricular diastolic waveform identified in our older subjects seemed to be qualitatively similar to, although not as severe as, those previously seen in patients with various cardiac diseases associated with diastolic impairment (including coronary artery disease, systemic hypertension, aortic valve stenosis, and hypertrophic cardiomyopathy.[2,3,5,6] Thus the results of our study are also relevant to the question of what should be considered to be a "normal" Doppler diastolic waveform. For example, if a large number of older people are included in a normal control population, then the range of values for the Doppler indices of left ventricular relaxation and filling will be increased, and this will reduce the sensitivity for detecting true abnormalities of diastolic performance. Similarly, because measures of diastolic function in older normal subjects may lie considerably outside the range seen in younger subjects, left ventricular diastolic impairment could be incorrectly identified in older individuals. These considerations suggest that values for Doppler indices of left ventricular diastolic performance measured in patients with cardiac disease should always be compared with those in age matched healthy controls.

Because coronary arteriography was not performed we cannot exclude unequivocally the possibility that some of our older subjects had clinically silent coronary artery disease. But coronary arteriography is unjustified and impractical in a healthy symptom free population such as ours. The changes in the Doppler diastolic waveform that we identified in the older volunteers were pronounced and consistent, however, and the occasional individual with silent coronary disease would not account for important differences in the pattern of flow velocity that we identified in the younger and older volunteers.

Left ventricular diastolic filling is a complex phenomenon influenced not only by the intrinsic properties of the cardiac muscle, but also by variables such as left ventricular mass and volume, systolic function, heart rate, and the loading conditions of the ventricle.[19-26] Since Doppler diastolic indices may be influenced by these multiple variables, the alterations in the diastolic waveform identified in our older study subjects do not definitively demonstrate that aging, per se, alters the primary intrinsic properties of the cardiac muscle (that is left ventricular relaxation and elastic properties of the ventricle). Data derived from our multivariate regression analysis do, however, support this hypothesis. For example, the multivariate linear regression analysis showed that age correlated significantly with most Doppler indices of left ventricular diastolic function, even after adjustment for left ventricular wall thickness and cavity dimension, percentage systolic shortening, or cycle length. Thus these data indicate that the effects of age on Doppler diastolic indices are independent of age related alterations in left ventricular morphology and function. Although all our study subjects had normal systemic blood pressure, left ventricular afterload was not measured directly. Thus a slight increase in left ventricular systolic load caused by reduced arterial wall distensibility[26] may have influenced transmitral flow velocity in our older subjects. Nevertheless, slight changes in systolic load do not seem to be sufficient to explain the size of the alterations in the left ventricular flow velocity waveform that we identified in older individuals.

In conclusion, our findings indicate that the Doppler left ventricular diastolic waveform is altered substantially by aging, and that age is an independent determinant of most indexes of left ventricular diastolic flow velocity. Thus the effects of age should be considered when the normal limits for Doppler indices of left ventricular diastolic function are defined.

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Reproducibility of cardiac output measurement by cross sectional and Doppler echocardiography

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SUMMARY The variability of Doppler echocardiographic estimation of cardiac output at the aortic orifice was investigated in eight healthy subjects. Cross sectional echocardiograms of the aortic orifice and aortic Doppler velocities were recorded and measured by four echocardiographers. Between subject variability was significantly larger than within subject variability for all variables. Variability owing to different echocardiographers and different measurement times was small compared with total variability. Coefficients of variation for aortic annular diameter, aortic velocity integral, and heart rate were 4·1%, 6·4%, and 5·0% respectively. The coefficient of variation for cardiac output was 8·8% and the 95% confidence interval for measurement of cardiac output by the Doppler method was 4·45 to 6·35 l/min. One echocardiographer reanalysed all the recordings and the results showed that recording the echocardiograms introduces a significantly larger source of error than measuring them.

Thus serial measurements of cardiac output by the Doppler method can be performed with acceptable reproducibility; this indicates that the technique can be accurately applied in clinical practice.

Cardiac output can be calculated from the blood velocity in the ascending aorta (measured by Doppler ultrasound) combined with aortic orifice area (measured by cross sectional echocardiography). The technique has been validated in various laboratory and clinical situations[1–3] and provides a simple and reliable method for the measurement of cardiac output without the need for vascular catheterisation.

To interpret Doppler flow measurements in clinical practice it is necessary to establish the variability of velocity and area measurements. Several studies have reported the variability of aortic velocity measurements,[4–6] but the variability of calculated cardiac output has been inadequately reported. This study investigated the variability of cardiac output measurement across the aortic valve in normal subjects. The contribution of the various sources of imprecision to the overall variability was determined and the 95% confidence interval for a single observation was estimated.

Patients and methods

Eight healthy people (six men, two women) aged 22–52 years (mean 28 years) were investigated. The procedure was explained to each subject and their informed consent was obtained. Measurements were made with the subjects in the semirecumbent position after they had rested for at least 15 minutes in a warm, quiet room. Cross sectional echocardiograms and continuous wave Doppler recordings were made on a Hewlett-Packard system (Model 77020A) with a 3·5 MHz phased array transducer and a 1·9 MHz dedicated independent continuous wave transducer. Recordings were made by four experienced echocardiographers. The order of investigation was randomised using a LS and the subjects remained recumbent throughout.

The diameter of the aortic orifice was measured during systole from cross sectional echocardiograms in the parasternal long axis plane.[7] Echocardiograms were recorded on videotape and then measured after completion of the velocity recordings by a freeze

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frame facility with superimposed calipers. Measurements were made from the leading edge of the anterior wall to the leading edge of the posterior wall. The diameters from five consecutive beats were averaged and the cross sectional area (CSA) was calculated from the equation $\Pi \times (D/2)^2$, where D = mean aortic diameter.

Blood velocity in the ascending aorta was recorded from the suprasternal notch by continuous wave Doppler ultrasonography. The direction of the ultrasound beam was adjusted until the highest velocities with the "cleanest" envelope were obtained. These velocities were taken to represent the velocities at the aortic orifice when the ultrasound beam was parallel with flow. The Doppler output and an electrocardiographic tracing were recorded on a strip chart at a paper speed of 100 mm/s. The area under the velocity curve, or the velocity integral (VI), was determined after each investigation by tracing from the baseline around the maximum velocity curve with a digitising tablet linked to a microcomputer.[8] Ten consecutive beats were averaged for each measurement.

Heart rate (HR) was measured directly from the RR interval of the simultaneously recorded electrocardiogram. Stroke volume (SV) and cardiac output (CO) were calculated as follows:

$$\text{SV (ml)} = \text{VI (cm)} \times \text{CSA (cm}^2\text{)}, \text{CO (l/min)} = \text{SV (ml)} \times \text{HR (min}^{-1}\text{)} - 1000.$$

The observers analysed their own recordings. Heart rate and velocity recordings were then numbered and reanalysed blindly out of order by one observer (SCR) to measure intraobserver variability. Because cross sectional echocardiograms were stored on videotape it was not possible to reanalyse them in random order. To try to eliminate any possible observer bias, recordings were reanalysed several weeks after the initial investigation.

STATISTICAL ANALYSIS

An analysis of variance was used to determine the contribution of various factors (variance components) to the overall variance. The total variance consists of a component owing to differences between the subjects (σS^2) and a component owing to differences within subjects (σW^2). The within subject variance is made up of a component representing the variability between echocardiographers (σE^2), a temporal component representing the variability between measurement times (σT^2), and a component representing the residual variability (σR^2). An approximate 95% confidence interval for a particular measurement on a typical subject was calculated as mean ± 2 σW. The confidence intervals calculated in this way relate specifically to the method used in this study which gives an average over a given number of cardiac cycles to reduce some of the within subject variability attributable to measurements from individual cardiac cycles. Coefficients of variation were determined from the within patient variance as $\sigma W \div$ mean.

An estimate of the contributions to the total variance of recording and of measuring the echocardiogram was obtained by calculating the differences between the initial measurements (performed by the four echocardiographers) and the repeat measurements (performed by one echocardiographer) for all recordings of the velocity integral, heart rate, and diameter. The variance attributable to measuring an echocardiogram was estimated from the standard deviation of the differences. This variance was then subtracted from the total variance for an estimate of the variance caused by the recording of the echocardiogram.

Results

Satisfactory diameter and velocity recordings were obtained in all eight subjects by each of the four echocardiographers. Investigations were completed in less than 30 minutes in each subject. Calculated Doppler cardiac output ranged from 4·59 l/min to 6·50 l/min.

Figure 1 shows the variance components for heart rate, velocity integral, and aortic diameter. Figure 2 shows the variance components for the calculated

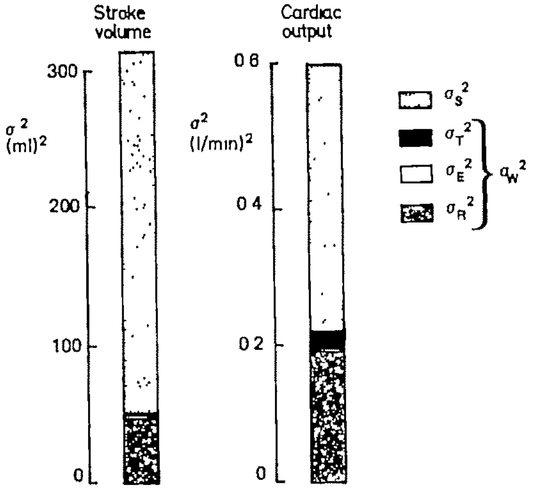

Fig 1 *Variance components for heart rate, velocity integral, and aortic diameter.* σS^2, *between subject component;* σW^2, *within subject component;* σT^2, *temporal component;* σE^2, *echocardiographer component;* σR^2, *residual component. See text for explanation.*

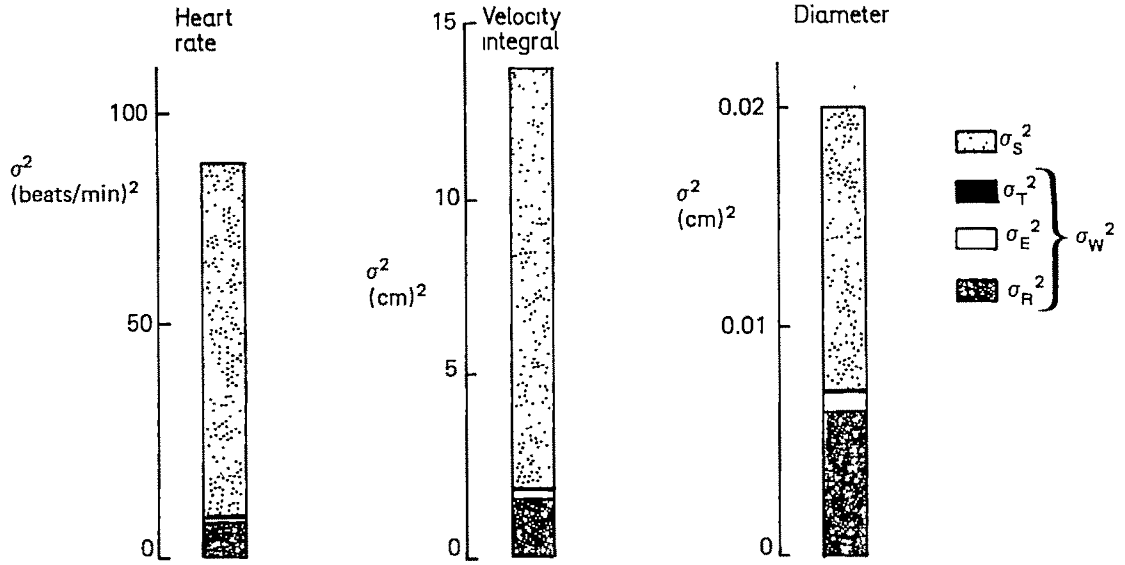

Fig 2 *Variance components for stroke volume and cardiac output.* σ_S^2, *between subject component;* σ_W^2, *within subject component;* σ_T^2, *temporal component;* σ_E^2, *echocardiographer component;* σ_R^2, *residual component. See text for explanation.*

variables stroke volume and cardiac output. For all variables the within subject variance was significantly smaller than the between subject variance ($p <$ 0·001). The "between echocardiographer" variance (σ_E^2) and the "between measurement times" variance (σ_T^2) were both small for all the measured and calculated variables and in no case were they significantly different from the residual variance (σ_R^2). The calculated within subject components shown in figs 1 and 2 are given for completeness, even though there were no significant differences.

Table 1 *95% confidence intervals and coefficients of variation for Doppler and cross sectional echocardiographic measurements*

	Mean	*2 SD*	*Coefficient of variation (%)*
Heart rate (beats/min)	63·4	6·4	5·0
Aortic velocity integral (cm)	23·4	3·0	6·4
Aortic diameter (cm)	2·17	0·18	4·1
Stroke volume (ml)	86·9	13·6	7·8
Cardiac output (l/min)	5·40	0·95	8·8

Table 2 *Variability owing to making and measuring Doppler and cross sectional echocardiographic recordings*

	Making echo (SD)	*Measuring echo (SD)*	*p*
Heart rate (beats/min)	3·1	0·4	<0·001
Aortic velocity integral (cm)	1·3	0·7	<0·001
Aortic diameter (cm)	0·07	0·05	<0·05
Stroke volume (ml)	5·0	4·6	NS
Cardiac output (l/min)	0·40	0·27	<0·025

Table 1 shows the mean and approximate 95% confidence intervals for each variable. Table 2 shows the contribution of recording and measuring the echocardiograms to the total within subject variance. The variance owing to recording the echocardiogram was significantly larger than the variance owing to measuring recordings for all variables except stroke volume. The variability of the one analyser who reanalysed his own recordings (intraobserver variability) was compared with the variability of the same analyser analysing the recordings of the other three analysers (interobserver variability) and no significant differences were found except for the measurement of velocity integral ($p <$ 0·005).

Discussion

This study reports the variability of Doppler measurements of aortic flow in a group of healthy adults. The echocardiographers were all experienced in obtaining and analysing Doppler velocity and cross sectional recordings and no attempt was made to select good echocardiographic subjects. Thus we hoped that the study would determine the size and source of error that might be expected in clinical practice.

We used a components-of-variance analysis to estimate the different possible sources of imprecision for each of the measurements. The results suggest that the variability caused by different observers obtaining and measuring echocardiographic recordings is small relative to the total variability. The variance owing to differences between the measurement times was also very small. By having one observer reanalyse all the recordings we were also able to determine that recording the echocardiograms is a significantly larger source of error than measuring them.

We believe that the present study is the first to report the reproducibility of measurement of aortic cardiac output by continuous wave Doppler. Lewis *et al* studied the interobserver reproducibility of measuring aortic flow by pulsed Doppler from the cardiac apex.[9] They reported a mean (SD) percentage error (difference between paired measurements expressed as a percentage of the mean of the pair) between the two observers of 6·8 (5·0)% for aortic stroke volume and cardiac output. With two observers, Ihlen *et al* obtained aortic continuous wave velocity recordings on two occasions one to 21 days apart.[10] All the recordings were then analysed by both observers. Aortic diameter was measured only once and this value was used for all later stroke volume calculations. The coefficient of variation between any pair of measurements in each patient was 9·2%, which is similar to that found in the present study. The coefficient of variation between the two observers was 0·1% and between the two measurement times it was 0·9%, confirming that interobserver and temporal variability contribute little to the overall variability.

Several previous studies have investigated the reproducibility of measurements of the velocity integral obtained from aortic continuous wave Doppler traces. Most studies have reported interobserver, intraobserver, and day to day variability, whether expressed as a mean percentage error or as a coefficient of variation, to be less than 6%.[5,6,11] Comparable figures have been reported for heart rate measurements.[6,12] The results of the present study are consistent with these findings.

Although several workers have investigated the change in aortic diameter during the cardiac cycle[13,14] this is the first study to report the variability of measurements of aortic annular diameter. Meijboom *et al*, in a study of Doppler mitral flow measurement, reported comparable variability for measurements of mitral diameter.[15] These findings suggest that although cross sectional echocardiographic diameter measurements are very reproducible, they are the largest source of error in Doppler flow measurements because the diameter has to be squared to obtain cross sectional area for flow calculation (the coefficient of variation for aortic area in the present study was 8·3%).

Probably the most clinically useful measure of reproducibility is the 95% confidence interval for a single measurement. This quantitates the size of change in an individual subject that is likely to represent a true haemodynamic change. Thus when different observers study unselected subjects, changes in cardiac output of more than 1 l/min cannot be accounted for by the variability inherent in the technique and are likely to represent a genuine change in cardiac output. This result resembles measurement of cardiac output by the dye dilution and thermodilution methods.[16,17] Satisfactory recordings were obtained in all subjects in the present study. Most previous studies have reported acceptable recordings in over 80% of patients with heart disease[1,18] although this fell to approximately 70% in ill patients undergoing haemodynamic monitoring in intensive care.[3,19] Nevertheless, in those subjects in whom satisfactory recordings are possible the Doppler method provides a simple, quick, and non-invasive technique for measuring cardiac output. The present results indicate that serial measurements, even if performed by different observers, are sufficiently reproducible to be useful in clinical practice.

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Importance of ancillary properties of β blockers in angina: a study of celiprolol and atenolol

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SUMMARY Celiprolol (400 mg) and atenolol (100 mg) were given once a day to 16 patients with stable angina pectoris in a double blind placebo controlled crossover study. Celiprolol produced less suppression of heart rate both at rest and during exercise than atenolol. Both drugs were equally effective in reducing the frequency of angina and in delaying the onset of ischaemia during exercise. Radionuclide ventriculography showed that atenolol but not celiprolol lowered cardiac output at rest and during exercise.

Thus the ancillary properties of celiprolol, including partial β_2 agonist activity and direct vasodilating activity, have detectable effects on cardiac function that may be beneficial in patients with angina.

The notable success of β adrenoceptor antagonists in the treatment of myocardial ischaemia in patients with coronary heart disease reflects the fact that effort is the main stimulus to the development of such ischaemia. There are some disadvantages associated with the principal therapeutic action of β blockade, which is suppression of the increase in heart rate and contractility that normally accompanies exercise.[1] These include an increase in left ventricular volume, which is energy wasting, and a reduction in cardiac output during exercise. Thus the interest in β blockers with ancillary properties that confer a more favourable haemodynamic profile while retaining the beneficial effect on myocardial ischaemia.

Celiprolol is a new β_1 selective adrenoceptor antagonist with partial agonist effects at the β_2 receptor and direct vasodilating activity. It is orally active, undergoes minimal hepatic metabolism, and is active for at least 24 hours when given in a dose of 400 mg.[2]

We compared the effects of a daily dose of celiprolol (400 mg) with that of atenolol (100 mg) on angina frequency, effort capacity, and indices of myocardial ischaemia and function at rest and during dynamic exercise in a double blind randomised crossover study of 16 patients with stable angina pectoris.

Patients and methods

PATIENTS

We studied 16 patients (14 men, two women; age range 28–69 years) with stable effort induced angina pectoris. Three had a previous history of myocardial infarction (all Q wave infarcts); none had sustained an infarct within six months of entry to the study. Patients with evidence of heart failure were excluded and the three patients with previous myocardial infarction all had values for resting left ventricular ejection fractions of $>40\%$. All 16 had angiographically proven coronary artery disease and a positive treadmill exercise test showing horizontal ST segment depression of at least 1 mm during exercise.

STUDY DESIGN

All antianginal treatment, except for glyceryl trinitrate was stopped over a run in period of one week. A single blind placebo period of one week was followed by two double blind treatment periods, each lasting two weeks, during which the patients were treated with atenolol (100 mg) and celiprolol (400 mg) once a day in random order. Assessments were made at the end of the placebo phase (day 7) and at the end of each two week treatment period (days 21 and 35). Exercise testing was carried out approximately six to eight hours after the last oral dose and a recovery period of at least one hour was allowed between the two exercise tests.

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ASSESSMENTS

The following assessments were made:

Angina frequency and glyceryl trinitrate consumption

Diary cards were issued together with a supply of glyceryl trinitrate and patients were asked to record episodes of angina and the number of glyceryl trinitrate tablets they took. Angina frequency and consumption of glyceryl trinitrate were analysed for the week before exercise testing in each of the three phases (that is days 0–7, 14–21, and 28–35).

Treadmill exercise testing

Heart rate and blood pressure were recorded before exercise in recumbent and standing patients. Symptom limited exercise testing was then performed with a Marquette CASE II system according to a modified Bruce protocol.

Radionuclide ventriculography

First pass radionuclide ventriculography (technetium-99m) was carried out with a Baird Atomic multi-crystal gammacamera both at rest and during upright bicycle exercise. Patients were exercised to a maximum during the single blind placebo phase and then to that same workload during the two treatment periods. One operator (JTW) did the analysis with standard software. Cardiac output was calculated from the product of heart rate, ejection fraction, and left ventricular end diastolic volume.

Statistical analysis

Results are given as mean (SE). The statistical significance of differences between treatments was measured by Student's *t* test for paired data. Appropriate correction was made for multiple comparisons (Bonferroni). Because three comparisons were made for most variables (placebo *vs* atenolol, placebo *vs* celiprolol, and atenolol *vs* celiprolol), significance was assumed at the level of $p < 0·02$.

Results

ANGINA FREQUENCY

Both atenolol and celiprolol reduced angina frequency significantly more than placebo (table 1); there was no difference between the two active drugs. Glyceryl trinitrate consumption was not significantly reduced by either drug.

Table 1 *Angina frequency and consumption of glyceryl trinitrate (GTN) (mean (SE))*

	Placebo	*Atenolol*	*Celiprolol*
Anginal episodes per week	10 (2)	5 (1)*	6 (1)*
GTN consumed per week	8 (2)	5 (2)	6 (1)

*p < 0·02, difference between placebo and drug.

Table 2 *Effects of atenolol and celiprolol on treadmill exercise testing (mean (SE))*

	Placebo	*Atenolol*	*Celiprolol*
Exercise time (s)	635 (48)	727 (52)	746 (49)
Maximum ST depression (mm)	2·4 (0·3)	1·9 (0·3)	2·1 (0·3)
Time to 1 mm ST depression (min)	7·4 (1·0)	10·2 (1·0)*	9·5 (1·2)*
Double product (/100) at 1 mm ST depression	190 (11)	125 (6)‡	151 (8)†§

*p < 0·02, †p < 0·005, ‡p < 0·001, difference between placebo and drug.
§p < 0·01, difference between atenolol and celiprolol.

EFFECTS ON HEART RATE AND BLOOD PRESSURE

The two active drugs differed markedly in their effects on heart rate and blood pressure. Whereas atenolol reduced resting heart rate by about 25% in both the supine and erect postures (table 2), celiprolol had no significant effect on resting heart rate. Atenolol significantly reduced systolic blood pressure in both lying and standing patients and also reduced diastolic pressure while the patient was standing; celiprolol had less effect on resting blood pressure and significantly reduced only standing diastolic pressure (table 2).

When patients were exercising on the treadmill both drugs significantly suppressed the tachycardia and the increase in blood pressure that occurred during exercise (figs 1 and 2). For simplicity, only the p values referring to differences between atenolol and celiprolol are shown. When patients were on atenolol the curve relating heart rate to exercise time generally paralleled the placebo curve, heart rates being approximately 25% lower at each stage of exercise on atenolol. When patients were treated with celiprolol, the curve relating heart rate and exercise time was flatter (fig 1); thus celiprolol had little effect on

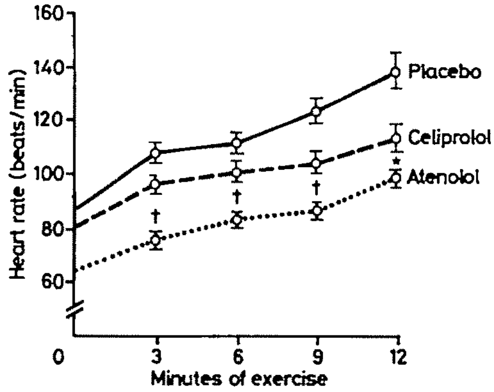

Fig 1 *Heart rate (mean (SE)) during treadmill exercise testing on placebo, atenolol, and celiprolol. Symbols refer to differences between atenolol and celiprolol (*p < 0·02, †p < 0·005).*

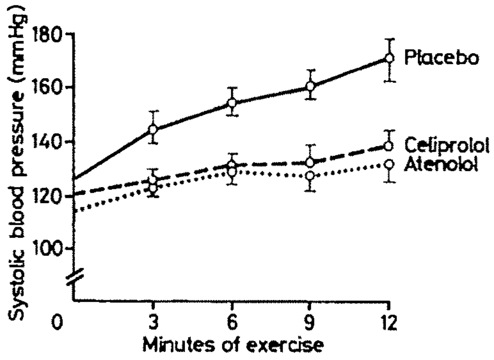

Fig 2 *Systolic blood pressure (mean (SE)) during treadmill exercise testing on placebo, atenolol, and celiprolol. There were no significant differences between atenolol and celiprolol.*

resting heart rate but did suppress heart rate as exercise progressed. Even at peak exercise, however, heart rate was significantly higher on celiprolol than on atenolol (120 (4) beats per minute *vs* 105 (4) beats per minute, $p < 0·005$).

The rise in systolic pressure on both drugs was lower than that on placebo, but there were no significant differences between the two drugs (fig 2).

EXERCISE CAPACITY AND ELECTROCARDIOGRAPHIC EVIDENCE OF MYOCARDIAL ISCHAEMIA

Mean exercise time on placebo was 635 (48) seconds. Exercise time was prolonged, but not significantly, by celiprolol (746 (49) s, $p = 0·031$ *vs* placebo) and by atenolol (727 (52) s, $p > 0·10$) (table 3). Maximum ST segment depression was not reduced by either drug (table 3), but both significantly delayed the onset of 1 mm ST segment depression; there was no significant difference between atenolol and celiprolol. The double product (heart rate × systolic blood pressure) at the onset of 1 mm ST depression was significantly lower on both drugs than on placebo and significantly higher on celiprolol than on atenolol (table 3).

Table 3 *Effect of atenolol and celiprolol on resting heart rate and blood pressure (mean (SE))*

	Placebo	*Atenolol*	*Celiprolol*
Lying:			
Heart rate (beats/min)	80 (2)	58 (2)†	74 (3)‡
Systolic BP (mm Hg)	131 (5)	117 (3)*	126 (4)
Diastolic BP (mm Hg)	88 (3)	75 (3)	82 (3)
Standing:			
Heart rate (beats/min)	87 (3)	64 (2)†	81 (3)‡
Systolic BP (mm Hg)	125 (5)	113 (3)*	119 (4)
Diastolic BP (mm Hg)	87 (3)	7 (2)*	81 (3)*

*p < 0·02, †p < 0·001, difference between placebo and drug.
‡p < 0·001, difference between atenolol and celiprolol

Table 4 *Effects of atenolol and celiprolol on left ventricular function (mean (SE))*

	Placebo	*Atenolol*	*Celiprolol*
Rest EF (%)	55 (2)	53 (2)	52 (2)
Exercise EF (%)	43 (3)	51 (3)†	49 (1)*
Change in EF	−13 (3)	− 2 (3)*	− 3 (2)‡

*p < 0·02, †p < 0·005, ‡p < 0·001, difference between placebo and drug
EF, ejection fraction

EFFECTS ON LEFT VENTRICULAR FUNCTION

The resting ejection fraction was 55 (2)% on placebo; during bicycle exercise this fell to 43 (3)% ($p < 0·01$). Atenolol and celiprolol had no effect on resting ejection fraction but both significantly ameliorated the fall in ejection fraction with exercise (table 4). Compared with placebo, atenolol but not celiprolol reduced cardiac output both at rest and during exercise (fig 3).

SIDE EFFECTS

No serious side effects were reported. One patient complained of lightheadedness while on atenolol and on celiprolol and one experienced fatigue on both atenolol and placebo.

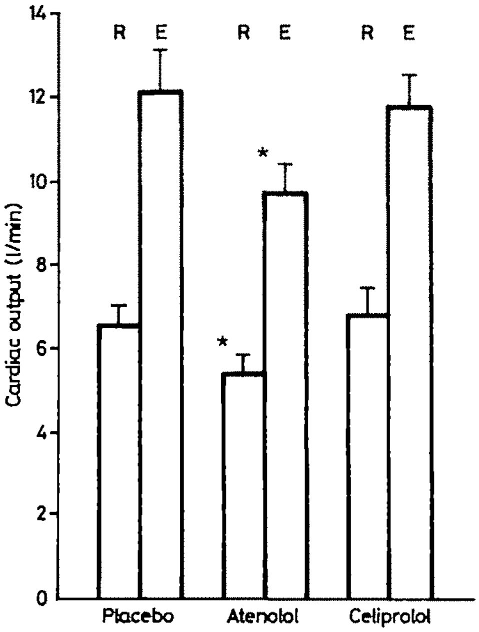

Fig 3 *Cardiac output (l/min) at rest (R) and during exercise (E) for the three treatment periods Compared with placebo, cardiac output was significantly reduced ($p < 0·02$) both at rest and during exercise by atenolol but not by celiprolol.*

The low frequency of side effects may reflect the fact that most of the patients had been treated with, and were tolerant of, β blockers before they joined the study.

Discussion

The major therapeutic action of conventional β blockers in angina pectoris is the suppression of exercise induced tachycardia, which leads to a reduction in myocardial oxygen requirement. β Blockers with intrinsic sympathomimetic activity produce less of a reduction in heart rate at rest and during exercise but may be less effective antianginal agents than β blockers without this property.[3] Figure 1 shows that celiprolol acts like a β blocker with intrinsic sympathomimetic activity; it had little effect on resting heart rate but produced considerable blunting of the exercise induced rise in heart rate. At peak exercise, heart rate and double product were significantly higher on celiprolol than on atenolol, yet both drugs were equally effective at reducing myocardial ischaemia during exercise as shown by electrocardiographic indices. Subjective testing showed that both drugs produced an equal reduction in angina frequency in keeping with previous studies that showed the antianginal efficacy of celiprolol.[4 5] There were, however, striking differences in their respective haemodynamic profiles, suggesting different mechanisms of action.

The product of heart rate and systolic blood pressure correlates with oxygen consumption.[6] Glyceryl trinitrate relieves angina by lowering the rate-pressure product,[7] but if the workload is further increased to raise this product to the baseline level, pain still occurs. The administration of β blockers, however, lowers the rate-pressure product at the onset of ischaemia by about 30%[8] suggesting an adverse effect on myocardial oxygen consumption for the same amount of cardiac work at a given pressure.[9] Table 3 shows that the rate-pressure product achieved for a similar degree of myocardial ischaemia on celiprolol was significantly higher than that on atenolol. The rate-pressure product on both drugs was lower than on placebo. This suggests that the ancillary properties of celiprolol have a beneficial effect on myocardial oxygen balance, either by increasing myocardial oxygen supply or by reducing demand. Several properties of celiprolol may contribute to this effect.

In patients with coronary artery disease drugs with intrinsic sympathomimetic activity produce less of an increase, or even a small fall, in systemic vascular resistance than drugs without such activity.[10] Thus the reduction in diastolic blood pressure on celiprolol might be explained by a fall in systemic vascular resistance whereas the reduction on atenolol probably reflects the fall in cardiac output. In addition, celiprolol seems to have a direct vasodilator action since its vasodilator activity is not abolished by blockade of β_2 agonist effects by propranolol.[11] Thus a reduction in afterload by intrinsic sympathomimetic activity and vasodilator activity might reduce oxygen demand and improve cardiac pumping in patients with ischaemic heart disease. Furthermore, in animal studies celiprolol had a positive inotropic effect that was not due solely to β_2 agonism as this effect also persisted in the presence of propranolol.[12]

Measurement of ejection fraction does not allow us to determine whether an observed rise is caused by increased contractility or to a change in loading conditions. Thus the ability to maintain a higher ejection fraction and cardiac output at a higher heart rate on celiprolol than on atenolol could be explained either by an increase in myocardial contractility or by afterload reduction mediated by both β_2 agonism and direct vasodilator activity. Whether these ancillary actions of celiprolol will be associated with a reduction in side effects of β blockade, particularly fatigue, remains to be seen.

In conclusion, celiprolol is an effective antianginal agent that seems to be well tolerated. It has less effect on heart rate than atenolol and does not reduce cardiac output either at rest or during exercise. These effects are probably related to its ancillary properties including β_2 agonism and direct vasodilator activity, which may be beneficial in ischaemic heart disease.

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Acute hepatitis after parenteral amiodarone administration

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SUMMARY Amiodarone is believed to have caused acute hepatitis 24 hours after intravenous administration in two patients in whom no other alternative cause of hepatitis was found.

Various extracardiac side effects have been reported after amiodarone treatment.[1 2] Asymptomatic hepatic dysfunction was reported in 15–40% of patients on long term amiodarone treatment.[3-5] These patients had increases in serum concentrations of transaminases of 1·5–4 times normal values.

We report two cases of acute hepatitis that developed 24 hours after intravenous amiodarone treatment. We found no other explanation for the hepatitis in these patients.

Case reports

PATIENT 1

A 48 year old woman (weight 50 kg) had undergone mitral and aortic valve replacement in 1982. She subsequently underwent repeat mitral valve replacement in February 1987. In May 1987 she was admitted as an emergency with a two month history of progressive dyspnoea, nausea, fatigue, and intermittent palpitation. She had been on long term treatment with frusemide, spironolactone, digoxin, and warfarin. On admission her blood pressure was 130/70 mm Hg, the jugular venous pressure was raised 6 cm, and she was peripherally well perfused. The apex beat was displaced and there was a soft apical systolic murmur. There was firm regular hepatomegly (three fingerbreadths). Her electrocardiogram showed atrial fibrillation with a ventricular rate between 140 and 180 beats per minute. Her chest radiograph showed mild cardiomegaly with pulmonary vascular redistribution. Doppler examination confirmed moderate mitral regurgitation and tricuspid regurgitation.

Table *Serum concentrations of hepatic enzymes and bilirubin in cases 1 and 2*

Day	*AP*	*AST*	*ALT*	*B*	*CK*
		Case 1 (50 kg)			
1	145	40	45	34	50
2	155	35	20	30	60
3	150	36	22	30	65
4 (amiodarone started)	185	40	28	30	70
5	150	720	580	65	55
6 (amiodarone stopped)	140	1860	1770	155	50
7	140	1010	1450	145	60
8	160	320	740	100	60
10	156	246	700	80	50
12	170	114	320	55	45
16	120	37	50	25	50
		Case 2 (54 kg)			
1 am	200	67	15	10	366
pm	210	71	27	12	908
2	240	259	47	15	1760
4	250	90	60	12	240
6 (amiodarone started)	220	45	25	20	100
7	500	2400	1440	60	90
8 (amiodarone stopped)	600	2400	1600	40	110
9	500	980	1340	35	150
10	—	450	770	30	120
12	250	200	210	30	160
13 operation					

Normal ranges for: AP, alkaline phosphatase (80–280 IU/l); AST, aspartate transaminase (12–48 IU/l); ALT, alanine transaminase (3–55 IU/l), B, bilirubin (3–22 μmol/l); CK, creatine kinase (30–150 IU/l).

The table shows the laboratory results. On day 1 she was started on verapamil 40 mg three times a day in addition to digoxin. This failed to control the ventricular rate and was stopped on day 3. On day 4 she still had fast atrial fibrillation despite adequate concentrations of serum digoxin. Treatment with intravenous amiodarone was started. She was given a bolus of 300 mg followed by an infusion of 900 mg. On day 5 900 mg of amiodarone was given intravenously and 400 mg orally and on day 6 200 mg was given orally. There was no significant change in her clinical condition despite a considerable rise in the serum concentration of hepatic enzymes. Toxic hepatitis was suspected and amiodarone was stopped. Other treatment was not changed. Serum concentra-

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tions of hepatic enzymes fell 24 hours after amiodarone was stopped. There was no change in her clinical condition. Propranolol (20 mg three times a day) was started on day 8 and the ventricular rate was rapidly controlled. The patient subsequently underwent mitral valve replacement. Other laboratory tests, including haemoglobin, urea, electrolytes, and erythrocyte sedimentation rate were normal. Hepatitis A and B markers, viral studies, and antitissue antibodies were negative. Blood cultures were sterile.

PATIENT 2

A 70 year old woman (weight 54 kg) was admitted with an acute inferior myocardial infarction. She had a past history of hypertension, angina, hypothyroidism, and polymyalgia rheumatica. She was taking atenolol, nifedipine, prednisolone, and thyroxine on admission. She had clinical and radiological evidence of left ventricular failure, blood pressure was 110/60 mm Hg, jugular venous pressure was elevated 7 cm, and her extremities were cool. The apex beat was displaced and there was auscultatory evidence of mitral regurgitation. There was firm regular hepatomegly (two fingerbreadths). Cardiac catheterisation showed evidence of pulmonary hypertension with a mean pulmonary capillary wedge pressure of 30 mm Hg, right atrial pressure of 14 mm Hg, and confirmed gross mitral regurgitation. She was treated initially with intravenous diuretics, sodium nitroprusside, and dobutamine 2·5 μg/kg/min. She remained unwell and on day 5 fast atrial fibrillation developed (160 beats/min). Intravenous amiodarone (300 mg) was given over 30 minutes, followed by 1200 mg over the next 24 hours. This dose (1200 mg/day intravenously) was continued until day 8 and then stopped because of an acute increase in the serum concentration of hepatic enzymes and once again a toxic hepatitis was suspected. Serum concentrations of hepatic enzymes fell rapidly when amiodarone was stopped. Her clinical condition remained poor and she underwent mitral valve replacement on day 12.

Discussion

Although we cannot exclude an alternative cause of hepatic dysfunction, we believe that the clinical course suggests that amiodarone was responsible for the development of acute hepatitis in these two patients.

Despite clinical evidence of cardiac failure both patients had normal concentrations of serum transaminases before the administration of amiodarone. There was no subsequent deterioration in their condition to account for the sudden increase in serum concentrations of transaminase or bilirubin. The suggestion that amiodarone caused the hepatitis is supported by rapid improvement in their liver function tests when amiodarone was stopped.

The increase in serum transaminases with long term amiodarone treatment was reversible and dose dependent, and did not require withdrawal of the drug.[1 2 6] There have been only two previously reported cases of possible acute hepatitis after intravenous amiodarone.[7 8] The mechanism of acute or chronic amiodarone hepatotoxicity is not known. There have been reports of both cytotoxic and cholestatic liver damage induced by amiodarone. It has been suggested that steatosis and alterations resembling alcoholic hepatitis or cholestatic hepatitis may represent short term side effects with oral treatment, whereas micronodular cirrhosis may be a long term side effect.[9]

The pattern of abnormalities in our patients is typical of hepatitis. Severe acute hepatic dysfunction with intravenous amiodarone is rarely reported and our two cases suggest that the liver is more susceptible to amiodarone toxicity when it is haemodynamically compromised or hypoxic.

Amiodarone is a popular antiarrhythmic agent because of its high efficacy in otherwise resistant arrhythmias and its freedom from any negative inotropic effects. In view of its widespread use, both intravenous and oral, it is important to be aware of any serious adverse reactions. We have reported these two cases to the Committee on the Safety of Medicines.

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Biventricular function in Friedreich's ataxia: a radionuclide angiographic study

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SUMMARY The systolic and diastolic function of both ventricles was assessed by radionuclide angiography in 21 patients with Friedreich's ataxia and hypertrophic cardiomyopathy. The indices of systolic function of the two ventricles and those of diastolic function of the right ventricle were generally normal. But in patients with Friedreich's ataxia the time to peak filling rate divided by the diastolic time of the left ventricle was significantly larger than normal. The increase correlated with the heart rate (r = 0·79) and this suggests an alteration in the timing of ventricle filling that is more evident at high heart rates. Movement of the left ventricle was little impaired; however, in 48% of the patients with Friedreich's ataxia the right ventricle showed evidence of hypokinetic segments.

Because there is a tendency for congestive heart failure to develop in patients with Friedreich's ataxia, this hypokinesis of the right ventricle should be monitored at follow up.

In earlier studies of left ventricular function in patients with Friedreich's ataxia we found: (*a*) a tendency for the pre-ejection period of the left ventricle to increase and for the ejection period to shorten, especially in patients with increased heart rates[1]; and (*b*) a significant reduction in left ventricular fractional shortening and ejection fraction of the left ventricle.[2] St John Sutton *et al* found that the diastolic function of the left ventricle, assessed by computerised M mode echocardiography, was abnormal in seven patients with Friedreich's ataxia.[3] Others reported a significant reduction in the thinning rates of the left ventricular posterior wall and interventricular septum in 13 patients with Friedreich's ataxia.[4]

The only scintigraphic studies of left ventricular function in patients with Friedreich's ataxia are those of Pentland and Fox[5] and Therriault *et al*[6] in which the ejection fraction was normal in most cases. We do not know of any radionuclide studies of the diastolic function of the left ventricle and the overall function of the right ventricle in this disease. We have assessed the function of both ventricles by radionuclide angiography in a group of patients with Friedreich's ataxia.

Patients and method

We obtained gated blood pool scintigrams from 21 patients (12 male patients and nine female patients; aged from 11 to 34, mean (SD) 19·5 (6·2)) in whom Friedreich's ataxia was diagnosed by Geoffroy's criteria[7] and in whom there was echocardiographic evidence of left ventricular hypertrophy. Neuromuscular impairment[8] was slight in six patients, moderately severe in three, and severe in 12. None had any signs of heart failure. The echocardiographic findings obtained in these cases (table 1) were compared with reference values from 50 healthy controls.

For the scintigraphic study we used a control group of eight healthy volunteers (five male and three female, aged from 12 to 38 (mean (SD) 21·5 (5·0)). Gated radionuclide angiography was carried out after in vivo labelling of the erythrocytes with stannous diethylenetriamine pentaacetic acid and intravenous injection of 750 MBq of technetium-99m pertechnetate. Ten minutes after injection of the tracer each patient was examined in the supine position with a large-field Anger scintillation camera equipped with a general purpose low energy parallel hold collimator connected on line to a minicomputer. A computer program gated to the electrocardiogram (SYMA, Elscint) collected and organised scintigraphic data into a series of 24 frames on a matrix of 64 ×

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Table 1 *Statistical comparison (Student's t test) of echocardiographic variables in healthy controls and in patients with Friedreich's ataxia*

	50 healthy controls	*21 cases of Friedreich's ataxia*	*p*
Age	23 8 (7 1)	19 5 (6 2)	NS
Body surface area (m^2)	1 4 (0 20)	1·5 (0 15)	NS
LVEDD (mm)	46 (3 6)	38 (5 3)	<0·01
FS %	39 (4 9)	36 (8 3)	<0·05
IVSTh (mm)	7·3 (1 3)	12 3 (4 1)	<0 01
LVPWTh (mm)	6 9 (1 1)	10 8 (1 5)	<0·01
RWTh	0 310 (0 05)	0 613 (0 11)	<0 01
LV mass index (g/m^2)	73 (16)	121 (50)	<0·01
IVSTh.LVP-WTh	1 1 (0 15)	1·1 (0 33)	NS

LVEDD, left ventricular end diastolic diameter; FS %, left ventricular fractional shortening; IVSTh, interventricular septum thickness; LVPWTh, left ventricular posterior wall thickness; RWTh, relative wall thickness; LV mass index, left ventricular mass index.

64 pixels that spanned the average cardiac cycle. The method has been validated for the assessment of the ejection fraction of both ventricles.[9 10]

We studied each patient in a left anterior oblique 35–45° projection and in a projection obtained by turning the crystal 40° counterclockwise. Twenty four points that were representative of the volume curve for each ventricle were transferred to a memory of a desk computer (Hewlett-Packard 85) and fitted with a Fourier series; the first four harmonics were usually retained.[11] The function obtained was differentiated to compute (fig 1) peak filling rate and peak ejection rate; the time to peak filling rate and time to peak ejection rate divided by the length of diastole and systole respectively were also calculated. Furthermore, we calculated the percentage of the stroke volume filled at the end of the rapid filling period and the percentage of the stroke volume filled at the end of atrial systole. We identified the end of the rapid filling period as point C on the derived curve.[12] The percentage stroke volume filled at the end of atrial systole was calculated as the difference between total stroke volume and the fraction filled at the end of the rapid filling period; the contribution of diastasis to the slow filling was discounted.

Regional wall motion was assessed by examining the parametric images obtained by Fourier analysis of scintigraphic data.[9] Regional right ventricular wall motion was analysed by end diastolic and end systolic isocontours. On the right ventricular outline we identified the anterior and inferior walls. On the left ventricular outline we defined the septal, apical, inferior, and posterolateral segments in the left anterior oblique projection, and the apical and inferior segments in the anterior projection.

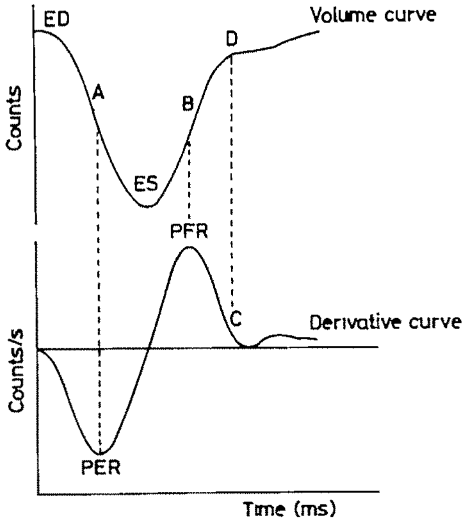

Fig 1 *The upper curve is a left ventricular volume curve obtained by equilibrium gated radionuclide angiography The lower curve is the first derivative of the left ventricular volume curve. Point A is the volume at which the peak ejection rate (PER) occurs. Point B is the volume at which the peak filling rate (PFR) occurs. Point C is the point after which 20% of the PFR occurs and represents the end of the rapid filling period. Point D on the volume curve represents the corresponding volume that marks the end of the rapid filling period. ED, end diastole; ES, end systole.*

Table 2 *Radionuclide variables describing left ventricular function (mean (SD))*

	Healthy volunteers (n = 8)	*Friedreich's ataxia (n = 21)*	*p*
Heart rate (beats/min)	64 (8)	77 (12)	<0 02
Ejection fraction (%)	71 (5)	75 (12)	NS
Peak ejection rate (EDV/s)	−3 30 (0 38)	−3 58 (0 74)	NS
TPER/ST	0·56 (0 04)	0 55 (0 05)	NS
ST/RR	0 40 (0 03)	0 41 (0 06)	NS
Peak filling rate (EDV/s)	3 55 (0 32)	3·35 (0 73)	NS
TPFR/DT	0 24 (0 06)	0·32 (0 08)	<0 025
% SV-RFP	88 (3)	89 (7)	NS
% SV-AS	12 (3)	11 (7)	NS

TPER/ST, time to peak ejection rate/systolic time, TPFR/DT, time to peak filling rate/diastolic time; % SV-RFP, percentage stroke volume filled at the end of the rapid filling period, % SV-AS, percentage stroke volume filled during atrial systole; ST, systolic time, RR, RR interval; EDV/s, end diastolic volume per second.

STATISTICAL ANALYSIS

All data are expressed as mean (1SD) with the 95% confidence limit as the range of normal values. All comparisons between patients and healthy controls were made by Student's *t* test and Bartlett's test was used to assess the homogeneousness of variances in the two groups; linear regression variables were calculated by the method of least squares.

Results

LEFT VENTRICULAR FUNCTION

Table 2 shows the data on left ventricular function. Indices of systolic function were usually normal, although the ejection fraction was greater than normal in nine patients and reduced (0·40) in one. The ratio of time to peak filling rate to diastolic time was higher in patients (mean (SD) 0·32 (0·08)) than in normal controls (mean (SD) 0·24 (0·06)). The increase correlated with increasing heart rate (r = 0·79); there was a 24% increase for each 10 beat/minute increase in heart rate (fig 2).

RIGHT VENTRICULAR FUNCTION

The data on right ventricular function in our patients (table 3) were not statistically significantly different from normal values.

WALL MOTION ABNORMALITIES

The frequency of wall motion abnormalities was different in the left and right ventricles (table 4). The left ventricle showed hypokinetic segments in three (14%) of our 21 patients, with 8 (7·6%) of 105 segments being affected. The right ventricle showed wall motion abnormalities in 10 (48%) patients, with 13 (31%) of 42 segments being hypokinetic. The alterations of right ventricle wall movement, however, were never severe enough to produce a statistically significant reduction in the ejection fraction. There were no akinetic or dyskinetic segments in either ventricle in any of our patients.

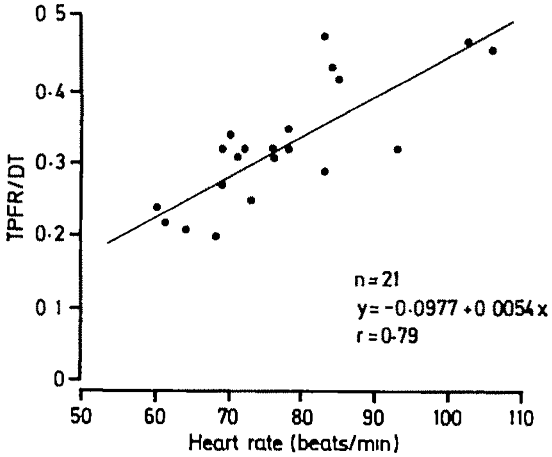

Fig 2 *Linear regression between heart rate and left ventricular time to peak filling rate divided by the diastolic time (LVTPFR/DT).*

Table 3 *Radionuclide variables describing right ventricular function*

	Healthy volunteers (n = 8)	*Friedreich's ataxia (n = 21)*	*p*
Heart rate (beats/min)	64 (8)	77 (12)	<0·02
Ejection fraction (%)	58 (8)	54 (13)	NS
Peak ejection rate (EDV/s)	−2·47 (0·46)	−2·25 (0·59)	NS
TPER/ST	0·57 (0·15)	0·54 (0·15)	NS
Peak filling rate (EDV/s)	2·73 (0·49)	2·30 (0·59)	NS
TPFR/DT	0·87 (0·20)	0·90 (0·27)	NS

TPER/ST, time to peak ejection rate/systolic time; TPFR/DT, time to peak filling rate/diastolic time, EDV/s, end diastolic volume per second.

Table 4 *Frequency of regional wall motion abnormalities of the left and right ventricles in 21 patients with Friedreich's ataxia*

	No of patients with hypokinesis (%)	*Total segments examined*	*Hypokinetic segments*
Left ventricle	3 (14)	105	8 (8)*
Right ventricle	10 (48)	42	13 (31)†

*Septal 2, apical 1, anterolateral, 1, posterolateral 2, inferior 2
†Anterior 10, inferior 3.

Discussion

In our series of patients with Friedreich's ataxia and hypertrophic cardiomyopathy, radionuclide angiocardiography of the left ventricle showed that overall systolic function was generally normal, as did Pentland and Fox (in 12 similar patients)[5] and St John Sutton *et al* (in seven patients examined by computerised M mode echocardiography).[3] The slight difference seen in our cases between the data obtained by M mode echocardiography and radionuclide angiography is not surprising in view of the different methods of calculating the ejection fraction. The radioisotope method is better, especially in patients like ours in whom movement of the interventricular septum and posterior wall of the left ventricle is abnormal.

Only one of the indices that we investigated (table 2) was significantly different in the patients with Friedreich's ataxia. This was the ratio of time to peak filling rate/diastolic-time interval, which was increased ($p < 0.02$); this was an average increase of 24% for each heart rate increase of 10 beats/minute (r = 0·79). This suggests that in patients with Friedreich's ataxia complicated by hypertrophic cardiomyopathy the timing of left ventricular filling is abnormal, with the defect being more evident at higher heart rates. The left ventricular peak filling rate was generally normal, and this result accords with the computerised echocardiographic study of St John Sutton *et al* in a series of seven cases[3] and with that of Casazza *et al* who studied 13 patients.[4]

Echocardiographic (especially M mode) assessment of the right ventricle is difficult; none the less, there are only a few angiographic studies,[13–15] generally of single cases of Friedreich's ataxia, showing hypertrophy of the right ventricle, sometimes associated with dynamic infundibular stenosis. Our radionuclide study showed that the systolic and diastolic function of the right ventricle is essentially normal in such patients despite the relatively frequent detection of regional hypokinesia, usually of the anterior wall. With allowance for possible diagnostic errors caused by the difficulty of distinguishing the free wall from the outflow tract of the right ventricle, this finding may be clinically important if it accounts for the evolution of congestive heart failure that complicates certain cases of Friedreich's ataxia.[16] It will be interesting to follow up our patients to see whether alterations in the movement of the right ventricle are associated with the development of congestive heart failure.

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Prediction of favourable responses to long term vasodilator treatment of pulmonary hypertension by short term administration of epoprostenol (prostacyclin) or nifedipine

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SUMMARY Eighteen patients with moderate to severe pulmonary hypertension were studied, nine with intracardiac shunts and nine without. The effects of an incremental infusion of epoprostenol (prostacyclin) (0·5–8 ng/kg per minute) or sublingual nifedipine (20–30 mg) were compared with the response to three months' treatment with oral nifedipine.

Both epoprostenol and sublingual nifedipine caused a fall in pulmonary vascular resistance and pressure and a rise in cardiac output. Patients with intracardiac shunts had higher systemic blood flows than those without shunts. Exercise in the shunt group was accompanied by systemic desaturation and hyperventilation. Analysis of individual results showed that the size of the response was inversely related to the severity of the pulmonary vascular disease. A good long term response to nifedipine seemed to be as readily predicted by the resting control values for haemodynamic variables as by values after short term treatment. A favourable response was likely if the pretreatment mean pulmonary artery pressure was <50 mm Hg, the ratio of total pulmonary to systemic resistance was $<0{\cdot}7$, or the ratio of mean pulmonary artery pressure to systemic artery pressure was $<0{\cdot}6$.

Short term vasodilator protocols may do harm. If such studies are carried out, an adequate dose range must be tried before the long term efficacy of an individual drug can be forecast.

Vasodilator treatment can produce a favourable haemodynamic response and improve exercise performance in some patients with pulmonary hypertension. In more advanced disease a vasodilator may be ineffective because pulmonary vascular obstruction has become fixed and there is no vascular reserve. In such patients these drugs may do harm. It is not known whether the response to short term treatment, if favourable, is predictive of long term benefit. In the few studies designed to answer this question patient numbers have been too small, there has been subselection of patients after the short term vasodilator trial, or failure to standardise the long term treatment.[1-3] When different vasodilators are evaluated the agents under test should be given to the same patients. Comparative studies suggest that some agents are better than others,[4-6] but none of these used a series of doses to cover the therapeutic range. There is therefore a need for a trial of the effects of vasodilator agents over a wide dose range to compare the short term and subsequent long term responses.

Patients and methods

METHODS

Table 1 shows the clinical details of the 18 patients we studied. All had normal resting left ventricular function (table 2) and were stable at the time of the short term study, although three had clinical evidence of right heart failure (patients 7, 8, and 9). The diagnosis of primary pulmonary hypertension required the exclusion of embolic and restrictive lung disease that could have contributed to the hypertension.[7 8]

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SHORT TERM STUDY

We tested fourteen patients (table 1). For two weeks before the study they were kept off drugs that affected platelet function or blood coagulation. They were fasted overnight and were given 10 mg diazepam as premedication. The variables given in the tables and figures were measured by standard cardiac catheterisation procedures. There was an interval of at least one hour between angiography and the first set of measurements. Pressures were measured by Statham P23 Gb transducers connected to an E for M VR12 recorder and averaged over one or more respiratory cycles.[9] Dextrose solution (5%) containing three units of heparin per ml was used to flush the lines. No more than one litre of fluid was given during the procedure. Caffeine containing drinks were not permitted.[10] Total blood loss for sampling did not exceed 200 ml.

Table 1 *Data on patients in the study*

Patient No	*Sex*	*Age (yr)*	*Disease classification*		*Extra-pulmonary shunt*	*$\dot{V}/\dot{Q}$ scan*	*Pulmonary angiogram*	*Short term*		*Long term exercise*
			Primary	*Secondary*				*Epoprostenol*	*Nifedipine*	
1	F	26	P			C	C	+	+	+
2	F	55	P			C	C	+	+	+
3	F	45	P			C	C	+	+	+
4	F	56	P	CRST*		C	C	+	+	+
5	F	41	P	SLE†		C	C	+	+	
6	F	30	P			C	C	+	+	
7	F	24	PE			C	C	+	+	
8	M	43	PE			C	C	+	+	
9	M	59	PE			C	C	+	+	
10	F	31	P PFO		+	C	C	+		+
11	M	22	P PFO	PE‡	+	NC	NC	+	+	+
12	F	34	E ASD		+	C	C		+	
13	F	50	E ASD		+	C	—	+	+	
14	F	24	E PDA		+	—	C	+	+	+
15	F	21	E VSD		+	—	C			+
16	M	20	E PDA + VSD		+	—	C			+
17	M	35	E PDA		+	—	C			+
18	F	23	E VSD		+	—	C			+

*Calcinosis, Raynaud's phenomenon, sclerodactyly, telangiectasis

†Clinically stable, inactive systemic lupus.

‡Previous episode of septic pulmonary emboli.

ASD, atrial septal defect; C, result consistent with diagnosis; E, Eisenmenger's syndrome; NC, result not entirely consistent with diagnosis (see text); P, primary pulmonary hypertension; PE, chronic pulmonary thromboembolism; PFO, patent foramen ovale; PDA, patent ductus arteriosus, VSD, ventricular septal defect; $\dot{V}/\dot{Q}$, ventilation perfusion lung scan.

Table 2 *Baseline values for short term study*

Patient No	*BSA (m^2)*	*VO_2 (%)*	*Sao_2 (%)*	*Hb (g/100 ml)*	*$\overline{PA}$ (mm Hg)*	*$\overline{SA}$ (mm Hg)*	*CI (l/min per m^2)*	*TPVRI (U.m^2)*	*SVRI (U.m^2)*	*RVEDP (mm Hg)*	*LVEDP or PCW (mm Hg)*
1	1·81	99·0	97·0	14·1	51	107	2·67	19·1	37·4	8	9
2	1·45	80·1	94·0	13·8	52	90	1·05	49·6	79·2	12	12
3	1·70	160·0	94·1	14·8	47	107	3·21	14·6	30·8	12	6
4	1·35	72·6	95·1	10·0	33·5	66	1·26	27·0	49·2	5	6
5	1·61	60·0	93·4	13·0	70	100	1·22	57·4	75·2	11	—*
6	1·64	87·4	95·3	13·5	62	78·5	1·73	41·8	41·8	7	5
7	1·85	110·0	94·4	14·8	62·5	91	1·27	49·2	59·0	18·5	12
8	1·74	77·3	88·5	12·4	67	78·5	0·93	72·0	67·1	16	4
9	1·92	92·5	93·0	15·4	52·5	86·5	1·25	42·0	51·6	25	8
10	1·79	102·9	82·5	16·0	103	78	2·96	64·1	65·0	9	5
11	1·79	103·5	90·9	17·1	84·5	88·5	1·87	50·0	33·7	15	9
12	1·50	—	74·0	17·3	(150/10)†	85	—	—	—	10	6
13	1·44	98·5	87·0	17·3	69	84·5	1·35	66·7	45·4	11	8
14	1·57	98·7	82·5	22·0	87·5	87·5	3·78	—	21·3	10	7

*No evidence of left ventricular failure on *x* ray or echocardiogram.

†Right ventricular pressure (mm Hg).

BSA, body surface area; CI, cardiac index; Hb, haemoglobin; LVEDP/PCW, left ventricular end diastolic pressure or mean pulmonary capillary wedge pressure, $\overline{PA}$, mean pulmonary artery pressure; RVEDP, right ventricular end diastolic pressure, Sao_2, arterial oxygen saturation; $\overline{SA}$, mean systemic artery pressure; SVRI, systemic vascular resistance index; TPVRI, total pulmonary vascular resistance index, Vo_2, oxygen consumption, % predicted.

Expired gas was collected with a Tissot spirometer or Douglas bag during the final three minutes of each treatment and control period. The volumes were corrected to standard temperature and pressure (dry) and the oxygen content was measured with a Centronic 200 MGA mass spectrometer. Arterial and mixed venous blood samples were drawn over the same period as gas collection, and oxygen saturation was measured by a CO-Oximeter 282. Control measurements were made before each of the three drug phases: (*a*) an epoprostenol infusion starting at 0·5 ng/kg per minute with the rate doubled every 15 minutes to a maximum of 8 ng/kg per minute; (*b*) a four hour epoprostenol infusion at a rate determined by the initial drug response, and (*c*) 10 mg sublingual nifedipine in three doses 20 minutes apart. The treatment order could not be randomised because of the long duration of action of nifedipine. There was a one hour interval between the successive periods of drug administration. Epoprostenol was prepared freshly in glycine buffer (pH 10·4) containing physiological saline solution to give a final pH of 9·5–10·0. The infusion was controlled by a Braun pump and given via the side arm of the catheter sheath into the right atrium. Nifedipine was given sublingually from a punctured 10 mg capsule shielded from the light.

LONG TERM STUDY

The maximum tolerated dose of oral nifedipine was given for three months. Treatment started in hospital and no other medication was given. At the end of three months, patients were exercised while on nifedipine and again one week after it had been stopped. The same protocol was followed on each visit. Patients were exercised on an Elema-Schonander bicycle ergometer with an increase in workload every minute.[11] The increase was adjusted for each patient so that at least three stages could be completed. The end points were inability to continue through fatigue or dyspnoea, clinically significant arrhythmias, or symptomatic hypotension.

Expired gases were collected and the volume measured by a Parkinson-Cowan dry gas meter, and the concentration of oxygen and carbon dioxide determined by the mass spectrometer. Arterial saturation was monitored with a Hewlett Packard 47201A ear oximeter.[12] Blood pressure was recorded by an arm cuff at the end of each one minute stage. Two exercise tests were performed one hour apart: in the afternoon (after no more than liquid refreshment in the previous four hours) and between three and six hours after the last dose of nifedipine. Patients rested for 15 minutes on the bicycle before each exercise test, and breathed through the mouthpiece for the last five minutes of the rest period. Measurements were made during the last 15 seconds of each minute of exercise. Gas volumes were corrected to standard temperature and pressure (dry).

Patient participation in the whole study was incomplete (table 1). Because of the risk and the likelihood of a negative response it was difficult to justify repeat cardiac catheterisation or short term vasodilator studies in patients in whom Eisenmenger syndrome had already been diagnosed. Patient 10 did not wish to continue to the nifedipine phase of the short term study. Those excluded from the long term trial had right heart failure and were severely disabled, had effort syncope, or were unable to attend.

STATISTICAL ANALYSIS

For the short term study we used two way analysis of variance with adjustment for missing values. Linear regression and Spearman's rank correlation was used for the subsequent exploration of individual data. For the long term study we used paired and non-paired Student's *t* tests, two tailed, for comparisons. Differences where $p < 0\cdot05$ were regarded as statistically significant.

Results

SHORT TERM STUDY

Epoprostenol

We studied 14 patients in the short term study (table 1) but we restricted the statistical analysis to the nine patients who did not have intracardiac shunts. Patients 6 and 13 had an appreciable fall in systemic pressure on the highest dose of epoprostenol and the infusion had to be stopped before completion of the last increment.

During the epoprostenol infusion there were progressive dose related decreases in average pulmonary and systemic arterial pressure and resistance and in the arteriovenous difference for oxygen. Cardiac output, heart rate, and oxygen consumption increased (fig 1, table 3). These changes were all statistically significant by analysis of variance ($p < 0\cdot001$). Arterial oxygen saturation did not alter (mean of 93·9 to 93·1%); this result was also found in the patients with shunts.

The responses varied. For each of the variables that were altered by the infusion, a significant part of the observed change was caused by interindividual differences (analysis of variance). Individual responses to epoprostenol were therefore analysed in the eight patients without shunts who received all the doses of epoprostenol up to and including 8 ng/kg per minute. The baseline haemodynamic variables of the patients showed a range of severity. In general, those with the highest total pulmonary vascular resistance index also had the highest systemic vascular resistance index and the lowest cardiac index and stroke volume index. A low cardiac index was associated with a low systemic blood pressure and resting oxygen consumption (fig 2a, b, e).

Figure 2 compares the pretreatment values with values on the highest dose of epoprostenol; three patients with shunts are included for comparison. The plot of the initial total pulmonary vascular resistance index against the final index shows a significant linear relation ($y = 1\ 16 + 0\ 46x$) and a

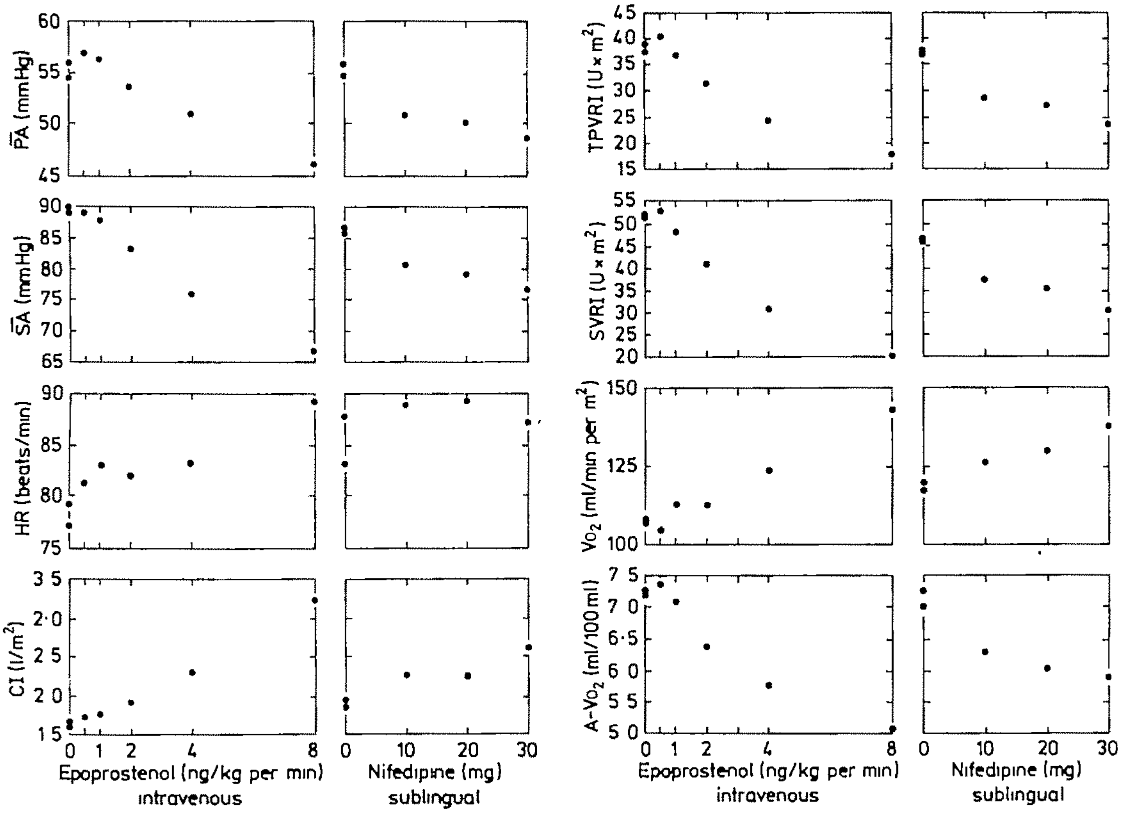

Fig 1 *Group responses to epoprostenol or nifedipine in the short term study of pulmonary hypertension. $\overline{PA}$, mean pulmonary pressure; $\overline{SA}$, mean systemic pressure; HR, heart rate, CI, cardiac index; TPVRI, total pulmonary vascular resistance index; SVRI, systemic vascular resistance index, Vo$_2$, oxygen consumption; A-Vo$_2$, arteriovenous oxygen content difference*

Table 3 *Drug effects (mean values) in short term study for the nine patients with no intracardiac shunts*

	Control		*Epoprostenol infusion (ng/kg per min)*					*Control*		*Sublingual nifedipine (mg)*		
	1	*2*	*0 5*	*1*	*2*	*4*	*8*	*1*	*2*	*10*	*10*	*10*
$\overline{\text{PA}}$	54 6	56 1	57 0	56 4	53 8	51 1	46 2	54 8	56 0	50 2	50 2	48 7
$\overline{\text{SA}}$	90 3	89 0	89 3	88 0	83 4	76 0	66 7	85 7	86 8	80 9	79 1	76 8
$\overline{\text{PA}}/\overline{\text{SA}}$	0 61	0 63	0 64	0 64	0 64	0 67	0 69	0 64	0 65	0 63	0 63	0 63
HR	79 4	77 3	81 4	83 3	82 2	83 3	89 2	83 1	87 9	88 8	89 2	87 1
CI	1 67	1 59	1 73	1 77	1 91	2 30	3 22	1 94	1 85	2 26	2 18	2 58
TPVRI	37 7	39 2	40 7	37 1	31 4	24 3	17 7	36 9	37 7	28 6	27 4	23 5
SVRI	51 5	51 8	52 4	48 0	40 9	30 6	19 9	45 8	46 1	37 2	35 2	30 0
TPVRI/SVRI	0 74	0 76	0 78	0 77	0 77	0 79	0 89	0 81	0 82	0 77	0 78	0 78
Vo$_2$	106 9	107 9	104 3	112 3	112 3	123 3	142 8	119 8	117 0	126 2	129 6	137 4
A-Vo$_2$	7 16	7 26	7 35	7 07	6 36	5 74	5 05	7 25	6 98	6 26	6 02	5 87

Vo$_2$, ml/min per m^2; A-Vo$_2$, arteriovenous difference in oxygen content (ml/100 ml) See table 2 for other abbreviations

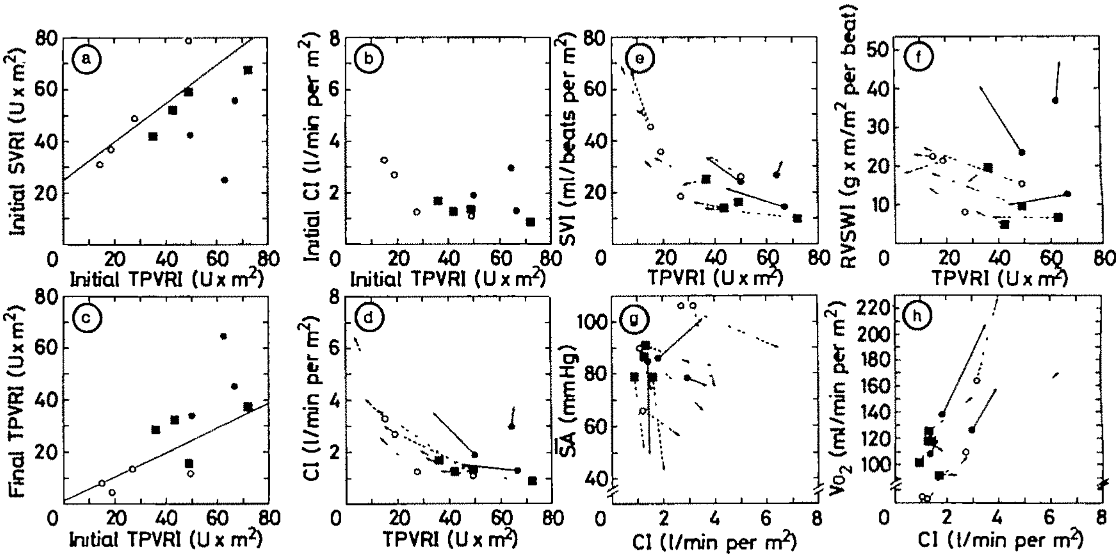

Fig 2 *Individual responses to epoprostenol (8 ng/kg per min) in the short term study.* ○, *responders;* ■, *non-responders;* ●, *patients with shunts. SVI, stroke volume index; RVSWI, right ventricular stroke work index. See legend to fig 1 for other abbreviations.*

Correlations:

Pretreatment	*Epoprostenol*	
(*a*) r = 0·82, p < 0·05	—	(Linear)
(*b*) r = −0·88, p < 0·01	—	(Rank)
(*c*) r = 0·71, p < 0·05	—	(Linear)
(*d*) r = −0·88, p < 0·01	r = −0·98, p < 0·005	(Rank)
(*e*) r = −0·79, p < 0·05	r = −0·98, p < 0·005	(Rank)
(*f*) r = −0·65, NS	r = −0·80, p < 0·05	(Linear)
(*g*) r = 0·75, p < 0·05	r = 0·69, NS	(Linear)
(*h*) r = 0·74, p < 0·05	r = 0·62, NS	(Linear)

slope less than that of the line of identity (fig 2c). The proportional reduction in pulmonary vascular resistance was generally greater in those with a lower initial resistance value.

The reduction in pulmonary and systemic resistance was accompanied by other changes in haemodynamic function that were usually proportional to the height of the initial pulmonary vascular resistance. Cardiac index and stroke volume index rose, especially in those patients with the lower initial values of total pulmonary vascular resistance index (fig 2d and e); the rise in oxygen consumption was also greater in these patients (fig 2h). Higher initial cardiac indices were associated with higher systemic pressure and oxygen consumption. The same was true at the end of the epoprostenol infusion (fig 2g and h). Right ventricular stroke work did not alter with epoprostenol (fig 2f).

Another method of displaying the individual changes in pulmonary vascular resistance is to plot pulmonary blood flow against pulmonary artery pressure under control conditions and at the highest dose of epoprostenol (fig 3). In all except one patient the slopes of the lines between the baseline and post-treatment values were less than the line of constant pulmonary vascular resistance. Thus all but one of the patients showed a reduction in pulmonary vascular resistance but, unfortunately, most showed no change in the ratio of pulmonary to systemic artery pressure throughout the range of epoprostenol doses examined (fig 4). In patient 1 the ratio fell (a favourable response) and in two (patients 5 and 6) there was a considerable rise in the ratio.

Five patients had a prolonged epoprostenol infusion. The dose ranged from 2 to 8 ng/kg per minute and the duration ranged from 40 minutes to three and a half hours. All developed symptoms, and in three this led to the drug being stopped. When the effect of the dose administered during the prolonged infusion was compared with the effect of the same dose during the initial part of the study, we found no significant differences in systemic blood flow (6·0 (3·4) and 5·1 (1·4) l/min), mean pulmonary artery pressure (66·8 (38·6) and 65·6 (39·7) mm Hg), or mean systemic pressure (78·8 (7·2) and 82·6 (15·3) mm Hg).

Nifedipine

The design of the study with nifedipine resembled that of the epoprostenol study. Doses were given sublingually at 20 minute intervals. Because nifedipine has a much longer half life than epopros-

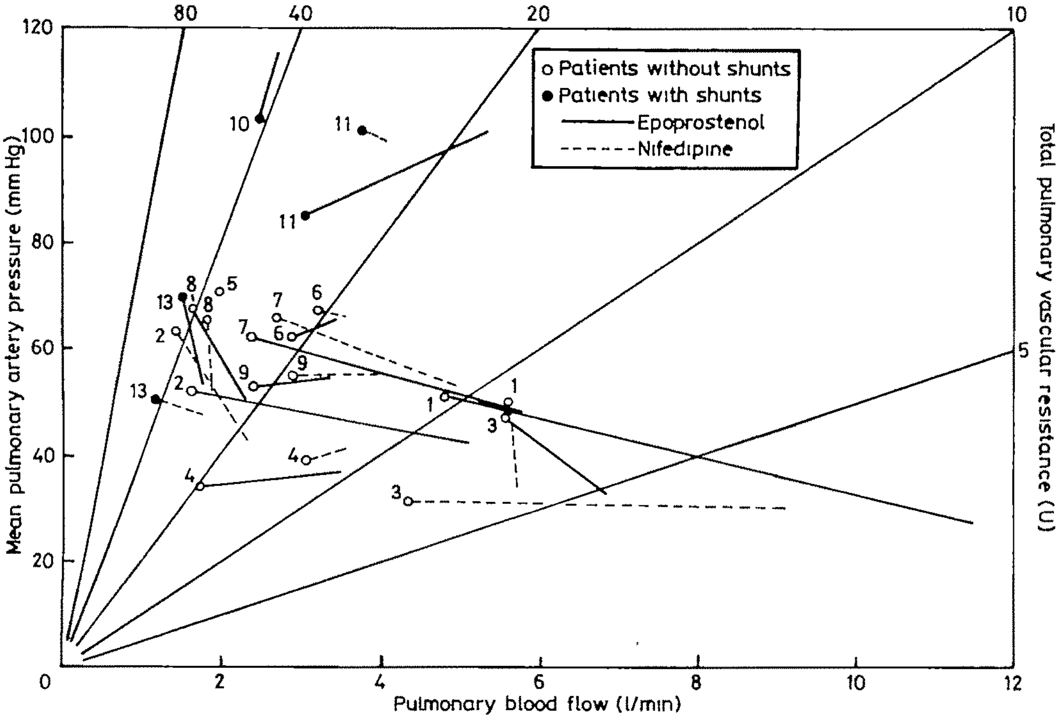

Fig 3 *Changes in pulmonary blood flow, pressure, and vascular resistance with epoprostenol or nifedipine in the short term study. Total pulmonary vascular resistance is displayed as lines of equal resistance (5–80 U). An unequivocally favourable response is indicated by a downward sloping line*

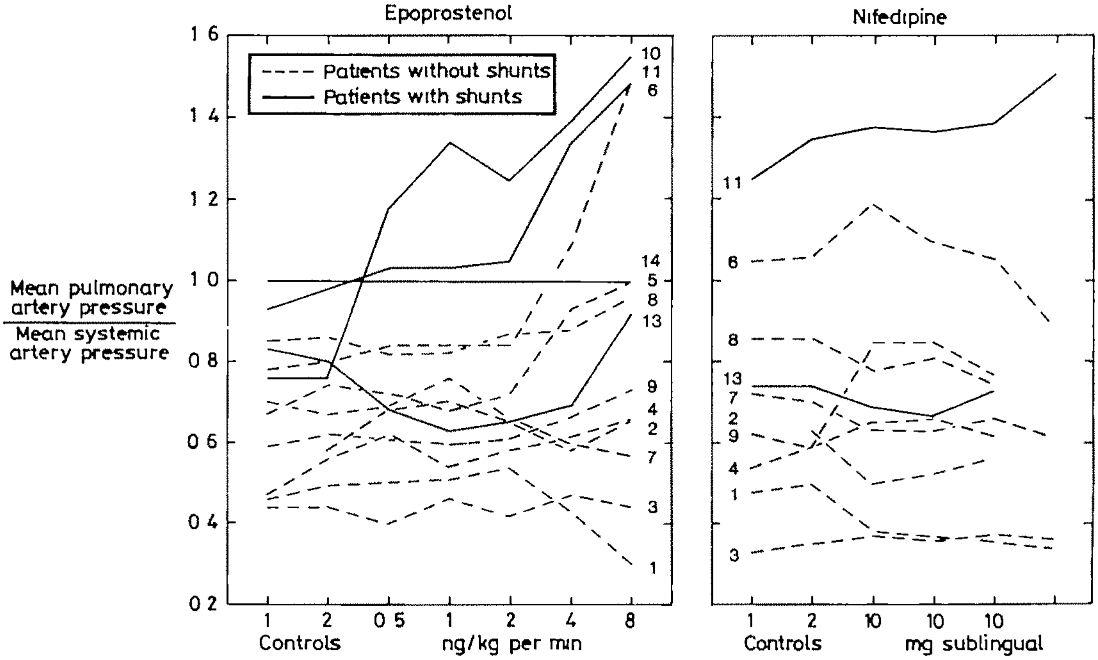

Fig 4 *Variation in individual response with drug dose in the short term study. Only patient 1 showed a fall in the ratio of mean pulmonary artery pressure to mean systemic artery pressure; a rise in output with no change in the ratio indicated a favourable response when the cardiac output rose. Patients with interatrial shunts responded badly, except patient 13. Patient 14, with a ratio of 1 throughout, had a patent ductus arteriosus.*

tenol, the action of the previous dose will have been carried over into the next dose. Thus dose-response curves must be interpreted with more caution.

The observed responses with nifedipine were in the same direction but were less pronounced than those with epoprostenol (figs 1, 3, and 4, table 3).

LONG TERM STUDY

Patients were subdivided into those with shunts and those without.

Exercise performance off nifedipine

Heart rate, mean systemic pressure, minute ventilation, and minute oxygen consumption ($p < 0{\cdot}05$ or less) rose both in patients with shunts and those without. There was a smaller fall in arterial oxygen saturation in those without shunts (2·8%, $p < 0{\cdot}05$) than in those with shunts (92·8 (2·6) to 69·1 (16·4)%, $p < 0{\cdot}001$). None had dizziness, syncope, or cardiac arrhythmias during bicycle ergometry. All were stopped by breathlessness. Patient 12 was not exercised because of a history of effort syncope[13]; her symptoms did not improve on nifedipine.

Effect of nifedipine on exercise performance

Only nifedipine was given in the long term study. The design was open and the exercise performance of 11 patients after three months of treatment was compared with that one week after nifedipine was stopped (table 1). The average maintenance dose was 34 mg daily (range 10 mg twice a day to 20 mg three times a day). The maximum tolerated dose was determined by side effects, particularly headaches and dizziness. None of the patients developed right heart failure. The size of the maintenance dose was not related to the degree of response. Long term treatment with nifedipine had no effect on arterial oxygen saturation. In patients without a shunt, nifedipine increased the heart rate at rest ($p < 0{\cdot}01$) but reduced the heart rate at peak exercise ($p < 0{\cdot}01$). There were no such effects in the shunt group. We saw no drug induced changes in systemic blood pressure.

On the basis of the best of the two exercise tests, the mean work performed for all the patients while on nifedipine was 264 (range 24 to 540) W and one week after stopping nifedipine it was 243 (range 32 to 420). Overall, these differences were not statistically significant but three patients (cases 1, 2, and 3) with relatively mild disease showed considerable deterioration in symptoms and decrease in work capacity of 54, 48, and 21% respectively after stopping nifedipine. The remaining eight showed no improvement in symptoms or work capacity (range +7 to −24%). Patient 4 had shown a similar favourable acute haemodynamic response to the first three patients (fig 3), and at first had a markedly improved exercise tolerance on oral nifedipine. Her deterioration three months later probably reflected progress of her disease. She is the subject of a previous report.[14] Patients 1 to 4 had a lower pulmonary artery pressure than the others in our series (table 2).

Patients 1 to 4 who responded to epoprostenol in the short term study—that is, they had a greater than 40% fall in total pulmonary vascular resistance with a dose of 8 ng/kg per minute—also responded to nifedipine in the long term study; however, patient 4 deteriorated towards the end of the three month period. Patients 7 and 8 who also responded to epoprostenol infusion were in right heart failure at the time of the short term study. Neither improved on oral nifedipine and neither was fit enough to exercise. The control haemodynamic values that were the best discriminators of patients who were likely to respond were a mean pulmonary artery pressure <50 mm Hg, a ratio of mean pulmonary to systemic pressure of <0·6, and a ratio of total pulmonary to systemic vascular resistance of <0·7 (figs 2 to 4).

Discussion

The main object of the study was to investigate the effect of two vasodilators on the pulmonary circulation in patients with severe obliterative pulmonary vascular disease and to identify those patients who were likely to respond favourably to vasodilator treatment. Both drugs reduced the pulmonary and systemic pressure; but the maximum effect of epoprostenol was greater than that of nifedipine. This may have been because the brief duration of action of epoprostenol permitted the infusion to be increased to the maximum tolerated dose, whereas the sublingual doses of nifedipine had a longer half life and the full effect was missed.

The fall in systemic arterial pressure was greater than the fall in pulmonary artery pressure, but when the ratio of pulmonary to systemic pressure was examined over the whole range of doses used there was no systematic change. When the results were taken together, there was no evidence of a selective effect of either drug upon the pulmonary circulation; that is pulmonary vascular resistance did not fall by a greater proportion than did the systemic resistance. Individual responses showed substantial variability and in one patient, who demonstrated the greatest beneficial response to vasodilators, there was a considerable fall in the ratio of pulmonary/systemic pressure during infusions of 4 and 8 ng/kg per minute of epoprostenol. Two patients without shunts and three with shunts at the atrial level, all of whom had severe disease, showed a rise in the ratio (fig 4).

As previous workers have shown, the improvement in cardiac output that is seen with vasodilators can be attributed to pulmonary vasodilatation[4 15 16]—pulmonary artery pressure falls only slightly.[17 18] Any depressant effect of nifedipine on right ventricular contractile force is thereby obscured. Indeed, right ventricular stroke work was maintained. The more pronounced fall in systemic than pulmonary artery pressure is likely to be a consequence of the absence of fixed disease in the resistance vessels of the systemic bed. Despite the rise in cardiac output there was a fall in systemic blood pressure. This suggests that the normal baroreceptor mediated mechanisms for maintaining systemic pressure were overwhelmed by the action of the vasodilators. The rise in cardiac output was also coupled to an increase in oxygen consumption. This has been seen before after the use of vasodilators in pulmonary hypertension.[19] The reason is not clear but perhaps oxygen use is greater after redistribution of flow within the tissues when cardiac output is restored. A further possibility is the energy cost of excessive ventilation. With both drugs there was hyperventilation, as judged by a small fall in arterial Pco_2 (not significant). It is noteworthy that in five of the patients without shunts resting pretreatment oxygen consumption was less than 90% of that predicted by the equation of LaFarge and Miettinen[20] (table 2).

Neither drug caused a significant change in arterial Po_2 or oxygen saturation, although one consequence of pulmonary vasodilatation in pulmonary vascular disease is an increase in the ventilation/perfusion mismatch. Any rise in mixed venous oxygen content resulting from an increase in cardiac output ameliorates this adverse effect.[21-23] The patient with shunts included in the short term study reacted differently from patients without shunts (figs 2 and 3). Vasodilator induced desaturation did not occur, suggesting that the rise in cardiac output, mixed venous oxygen saturation, and ventilation accompanying systemic vasodilatation was sufficient to prevent this despite an increase in right to left intracardiac shunting.

The similarity in the reactions to the two drugs used in this study and the way these altered in a systematic fashion with dose demonstrate the need for adequate dose comparison before it can be concluded that one vasodilator is useful to a patient and another ineffective or dangerous. The maximum dose of nifedipine used in the long term study was limited by side effects that may have been drug specific rather than consequences of the haemodynamic response.

A good response to a vasodilator drug is seen as a rise in cardiac output or a fall in pulmonary artery pressure or preferably both. When there is only a slight response the increase in right ventricular output may result in maintenance of a high pulmonary artery pressure, as was seen in most of our patients. A vasodilator drug with a positive effect on right ventricular contractile force may cause a rise in pulmonary artery pressure despite pulmonary vasodilatation.[24] Conversely, pulmonary artery pressure can fall without pulmonary vasodilatation, as a result of a fall in output caused by depression of right ventricular function.[5] That this was not seen with nifedipine suggests that the afterload was reduced by pulmonary vasodilatation in each patient and that this outweighed any depressant effect on the right ventricular myocardium. Nifedipine is known to relax isolated human intrapulmonary arteries.[25] In another patient, not in this study, administration of nifedipine induced acute right ventricular failure in a man with chronic thromboembolic pulmonary hypertension.

The long term study was open both for ethical reasons and because nifedipine induced symptoms such as headache and flushing in all the patients. The dose of nifedipine was titrated before the patient left hospital. Only four patients showed a favourable response to long term nifedipine and in the fourth patient the improvement was not maintained, probably due to progression of her disease. These four patients had responded favourably to epoprostenol in the short term study. Because the two patients with right heart failure who responded to epoprostenol did not improve with the long term administration of nifedipine, it seems that the long term response could be predicted more accurately from resting haemodynamic variables than from the effect of epoprostenol.

We suggest that short term vasodilator studies should be avoided where possible because they provide little additional information. A favourable response to the long term administration of nifedipine can be expected in patients with primary pulmonary hypertension whose disease is mild or moderate but not in those in whom it is advanced. Only three patients with chronic thromboembolic pulmonary hypertension were tested; none of them responded well in the long term. It is probable that the obstruction to pulmonary blood flow in such cases is much more mechanical rather than vasospastic. None of the patients with the Eisenmenger syndrome responded favourably; they had higher calculated pulmonary vascular resistance than the patients with pulmonary hypertension and no shunts.

We do not know whether long term benefit from nifedipine will remove the need for, or indefinitely postpone, heart-lung or lung transplantation in patients with primary pulmonary hypertension who are diagnosed and treated early[3] but this seems unlikely.[26] The disease usually becomes worse.[27] It seems probable that unless the pulmonary artery pressure can be made to fall the disease process will continue to advance[28] and that amelioration of the patient's symptoms by the rise in output will prove to be temporary.[29] With our present knowledge, we believe that patients with severe disability, unfavourable haemodynamic features, and particularly those with right ventricular failure, should not be denied transplantation in the hope that they will benefit from vasodilator treatment. There may, however, be a role for vasodilator treatment in patients awaiting heart-lung transplantation.[29]

Conclusions

The short term actions of epoprostenol and nifedipine in patients with severe pulmonary hypertension were very similar. Criteria for the prediction of a favourable clinical response to oral nifedipine were evaluated and resting haemodynamic variables were found to be as useful as the responses to short term treatment in the patients studied. Failure to titrate the dose has in part been responsible for a false impression that one vasodilator agent is effective when another is not[30]. Epoprostenol seems to have no advantage over nifedipine that would justify attempts to use this drug for long term treatment with all the attendant difficulties, hazards, and costs of prolonged intravenous treatment.

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Transient abnormal septal motion after non-surgical closure of the ductus arteriosus

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SUMMARY Abnormal septal motion on M mode echocardiography was seen in eight of 16 patients soon after non-surgical closure of the ductus arteriosus. Ten to twenty-nine months after the procedure the abnormal septal motion had disappeared spontaneously. The cross section of the left ventricular cavity was circular both when septal motion was abnormal and when it was normal. Cross sectional echocardiography showed that there was an exaggerated anterior swinging motion of the heart in systole in patients with abnormal septal motion on the M mode recordings. The left ventricular end diastolic diameter before closure was significantly larger, and its reduction after closure was more pronounced in those with abnormal septal motion than in those without. This suggested that the abnormal septal motion was associated with relief of long standing left ventricular volume overload. It is suggested that acute shrinkage of the heart caused temporary laxity of the pericardium, and consequently more movement of the heart within the thorax. The return of normal septal motion suggests that the pericardium gradually shrank to accommodate the smaller heart.

Abnormal motion of the interventricular septum is seen in M mode echocardiograms recorded in right ventricular volume overload,[1-3] pericardial disease,[4-8] intraventricular conduction disturbance,[9 10] ischaemic heart disease,[11-14] or after open chest cardiac surgery.[15 16] We found transient abnormal septal motion in patients who had a ductus arteriosus closed by a catheter plugging method,[17 18] which does not require thoracotomy.

Patients and methods

Sixteen patients (four men and 12 women; aged 19–58 (mean 38)) had non-surgical closure of the ductus arteriosus with a plug guided by catheters.[17 18] This method is not suitable for patients with severe pulmonary hypertension. No patient had an intraventricular conduction disturbance, either before or after the procedure.

Echocardiographic examinations were performed 1–51 days (10 (12)) before and 1–13 days (7 (3)) after the ductus arteriosus had been plugged. Six patients were also examined 10–29 (16 (7)) months after closure.

We used a Toshiba SSH-11A or SSH-40A echocardiograph (both with a 2·4 MHz transducer). M mode echocardiograms were recorded by a Toshiba LSR-20A strip chart recorder at a paper speed of 50 mm/s. Cross-sectional echocardiograms were recorded by a Victor BR-6400 video-tape recorder for subsequent frame analysis. The patients were examined in the left oblique decubitus position, at held expiration during normal breathing. The transducer was manipulated to obtain the short axis view of the left ventricle at the level of the tip of the papillary muscle. We took care to get a cross section that was perpendicular to the long axis of the left ventricle and on which the endocardial surface was clearly defined. After the real time images had been recorded on video tape, the ultrasound beam was directed to the centre of the left ventricle and the M mode echocardiogram was recorded. We compared this technique with the standard technique for echocardiographic recording of interventricular septal motion.

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MEASUREMENTS

The systolic excursion of the interventricular septum was measured, with the leading edge of the left side of the ventricular septum as the reference point. The systolic phase was defined as the time from a peak of the R wave of the electrocardiogram to the time when the left ventricular posterior wall was in its most anterior position. A negative or zero value for the systolic excursion was regarded as abnormal motion. The left ventricular diameter was measured at end diastole and end systole. The right ventricular diameter was measured as the distance from the right ventricular endocardial echoes to the right side of the ventricular septum on an end diastolic recording. The left atrial diameter was measured on the M mode echocardiogram.

Cross sectional echocardiograms were reviewed frame by frame on a video digitiser connected to a Hewlett Packard model 9845T desk top computer. It is known that the left ventricular cavity is deformed by right ventricular volume overload.[19] To examine this deformation, the circumferential length and area of the left ventricle at end diastole and end systole were calculated by digitising the endocardial surface of the left ventricle.

$$\text{Deformity index} = (\text{Ac}-\text{A})/\text{Ac} \times 100\ (\%)$$

where A is the cross sectional area of the left ventricular cavity and Ac the area of an assumed full circle of the same circumference as that for the actual area measured. The distance of the centre of gravity of the cross sectional area of the left ventricle from the anterior chest wall was calculated automatically by the same digitising method. This is referred to as the centre of the heart. The systolic excursion of this centre was calculated from its end diastolic and end

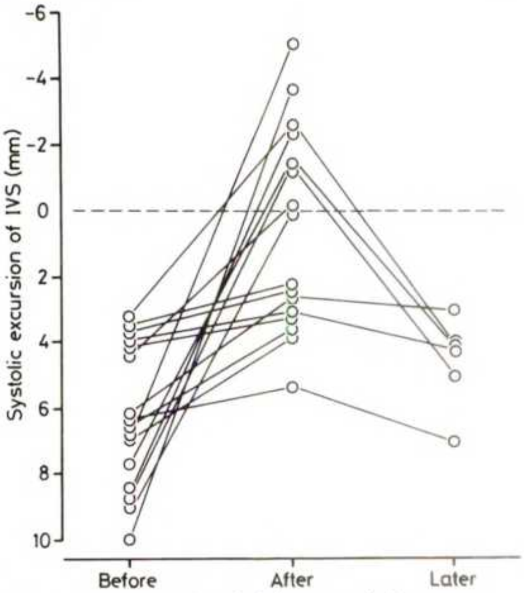

Fig 2 *Systolic excursion of the interventricular septum (IVS) before closure, soon after closure, and later. Anterior excursion is shown as a negative value. Half the patients showed abnormal septal motion soon after closure but none of the six examined showed it later.*

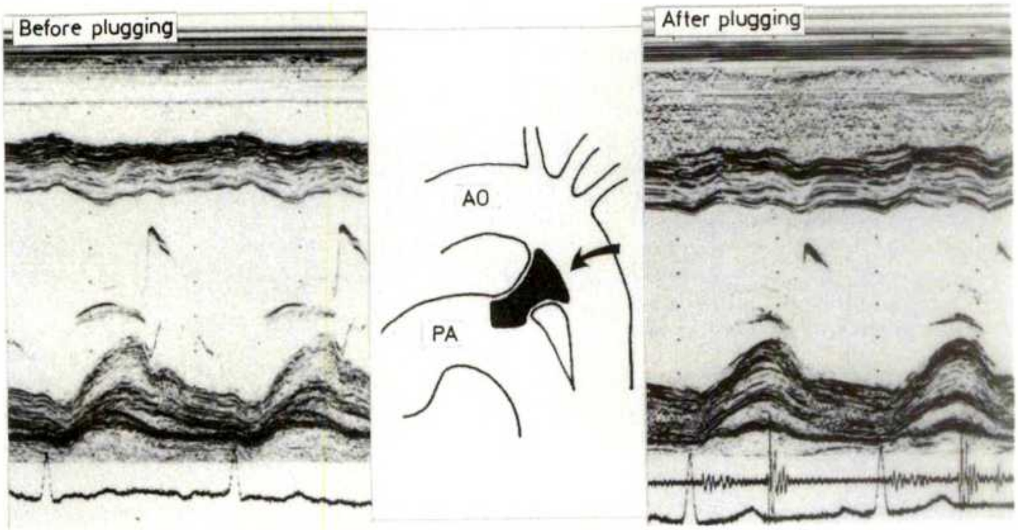

Fig 1 *Representative M mode echocardiograms before and soon after closure of the ductus arteriosus by the plugging method (shown schematically in the middle panel). There was abnormal septal motion after closure of the ductus but not before. AO, aorta; PA, pulmonary artery.*

Table 1 *Echocardiographic data (mean (SD)) before (A and C) and after (B and D) the closure of the ductus arteriosus in patients showing abnormal septal motion (group 1) and normal septal motion (group 2) soon after the procedure*

	Group 1		*Group 2*		*p value*			
	A	*B*	*C*	*D*	*Av/B*	*Cv/D*	*Av/C*	*Bv/D*
IVSex (mm)	7·2 (2·3)	−2·1 (1·7)	5·0 (1·3)	3·3 (0·9)	0·005	0·005	0·05	0·001
LVDd (mm)	60 (3)	49 (4)	53 (5)	48 (5)	0·005	0·005	0·01	NS
LVDs (mm)	40 (3)	39 (4)	33 (3)	33(4)	NS	NS	0·01	0·02
LAD (mm)	41 (6)	36 (6)	32 (4)	29 (5)	0·005	NS	0·01	0·02
RVDd (mm)	14 (3)	18 (5)	16 (5)	19 (5)	0·025	0·025	NS	NS
Cex (mm)	0·5 (1·4)	5·3 (2·1)	1·9 (1·2)	3·3 (1·5)	0·005	0·025	0·1	0·05
DI	3·8 (0·8)	3·9 (0·4)	4·2 (1·2)	4·5 (1·0)	NS	NS	NS	NS

IVSex, excursion of interventricular septum; LVDd, left ventricular end diastolic diameter; LVDs, left ventricular end diastolic diameter; LAD, left atrial diameter; RVDd, right ventricular end diastolic diameter, Cex, excursion of the "centre of gravity" of the cross section of the left ventricle; DI, deformity index of the left ventricle.

systolic position, and this was used to express the entire motion of the heart.

Measurements from M mode recordings and from the cross sectional recordings were performed independently by two examiners. The mean of 3–5 cardiac cycles was calculated for all measurements.

The patients were divided into two groups according to septal motion within two weeks of closure: group 1 had abnormal septal motion and group 2 did not.

The difference of the values obtained before and after closure in the same subjects was analysed by the paired *t* test and the difference between the two groups was analysed by Student's *t* test. Data were expressed as mean (SD), and a p value of < 0·05 was regarded as statistically significant.

Results

Before closure of the ductus arteriosus septal motion was normal in all patients. Soon after closure systolic septal excursion was found to be reduced in all patients. As a result, eight patients were placed in group 1 and the other 8 in group 2 (figs 1 and 2). Before closure the systolic excursion in group 1 had been larger than that in group 2 (table 1). Thus the more exaggerated the posterior movement of the interventricular septum before closure, the more anteriorly the septum moved after closure (fig 2). Several months after closure, septal motion had returned to normal in all patients.

Peak and mean pulmonary artery pressure before closure were almost normal, and there was no difference between the groups 1 and 2. The pulmonary to systemic flow ratio was larger in group 1 than in group 2 (table 2). Because the flow ratio was 1·0 after closure, its change was larger in group 1 than in group 2. Cardiac output was similar in the two groups. The peak pressure of the left ventricle was higher in group 1 than in group 2.

Before closure the left ventricular end diastolic and end systolic diameters and left atrial diameter were

Table 2 *Haemodynamic data (mean (SD)) before closure of the ductus arteriosus in patients showing abnormal septal motion (group 1) and normal septal motion (group 2) after the procedure*

	Group 1	*Group 2*	*p value*
LV	142 (11)	113 (17)	0·01
PA	31 (7)	25 (5)	NS
PAm	21 (8)	16 (4)	NS
CI	4·2 (1·4)	3·0 (0·4)	NS
Qp/Qs	2·1 (0·4)	1·6 (0·2)	0·05

LV, left ventricular systolic pressure; PA, systolic pulmonary arterial pressure; PAm; mean pulmonary arterial pressure; CI, cardiac index; Qp/Qs, pulmonary to systemic flow ratio.

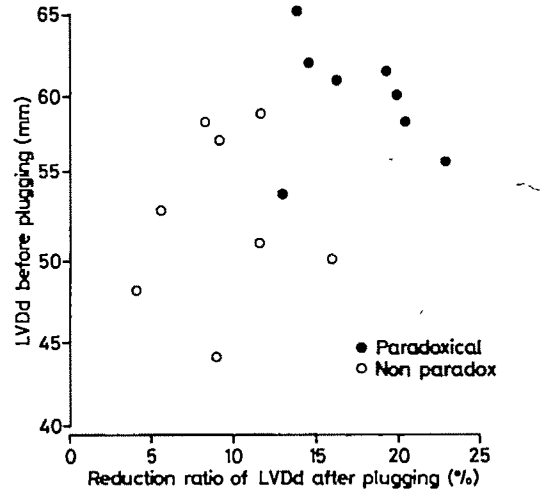

Fig 3 *Correlations of left ventricular end diastolic diameter (LVDd) before closure and its reduction ratio soon after closure of the ductus. Patients with abnormal motion of the interventricular septum (●) had different results from those without (○).*

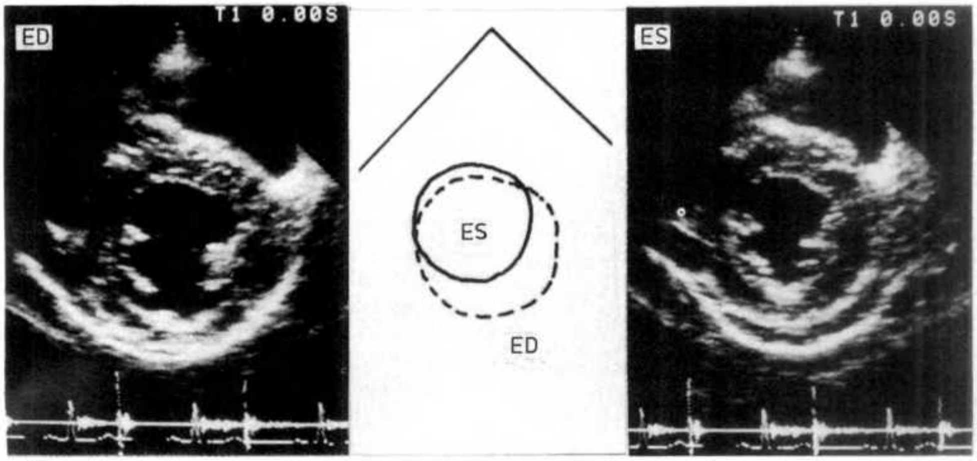

Fig 4 *Short axis view of the left ventricle soon after closure of the ductus. This patient showed abnormal septal motion in M mode echocardiograms. The left ventricular cavity was circular at both end diastole (ED) and end systole (ES). The left ventricle moves anteriorly in systole, as indicated by the overlapping images of the endocardial traces at end diastole (broken line) and end systole (solid line).*

significantly larger in group 1 than in group 2 ($p < 0{\cdot}01$ in each) (table 1). This difference was compatible with the difference in pulmonary to systemic flow ratio between the two groups. After closure, the left atrial diameter became significantly smaller in group 1 ($p < 0{\cdot}005$) but was unchanged in group 2. The left ventricular end diastolic diameter became significantly ($p < 0{\cdot}005$) smaller in both groups (by 18 (3)% in group 1 and by 10 (4)% in group 2; $p < 0{\cdot}001$).

We believe that septal motion became abnormal because the large left ventricular cavity that was present before closure was considerably reduced after closure of the ductus (fig 3).

The sizes of the right ventricular diameter before and after closure were similar in the two groups; and in both groups right ventricular diameter increased after closure ($p < 0{\cdot}025$) (table 1). The short axis cross sectional echocardiogram showed that the left ventricular cavity was almost circular throughout the cardiac cycle in all patients both before and after closure (fig 4). The deformity index of the left ventricle was similar before and after closure in groups 1 and 2 (table 1). These results indicate that deformation of the left ventricular cavity was not the cause of the abnormal septal motion.

The short axis view showed that the left ventricle moved anteriorly in systole in group 1 after closure (fig 4). The centre of the heart moved anteriorly in systole in both groups even before closure, though the magnitude of this movement was not significant. After closure of the ductus arteriosus the systolic anterior excursion increased significantly in both groups, but there was a larger increase in group 1 than in group 2 (table 1). This exaggerated anterior excursion did not persist; it was not seen 10–29 (mean 16(7)) months after closure. The systolic excursion of

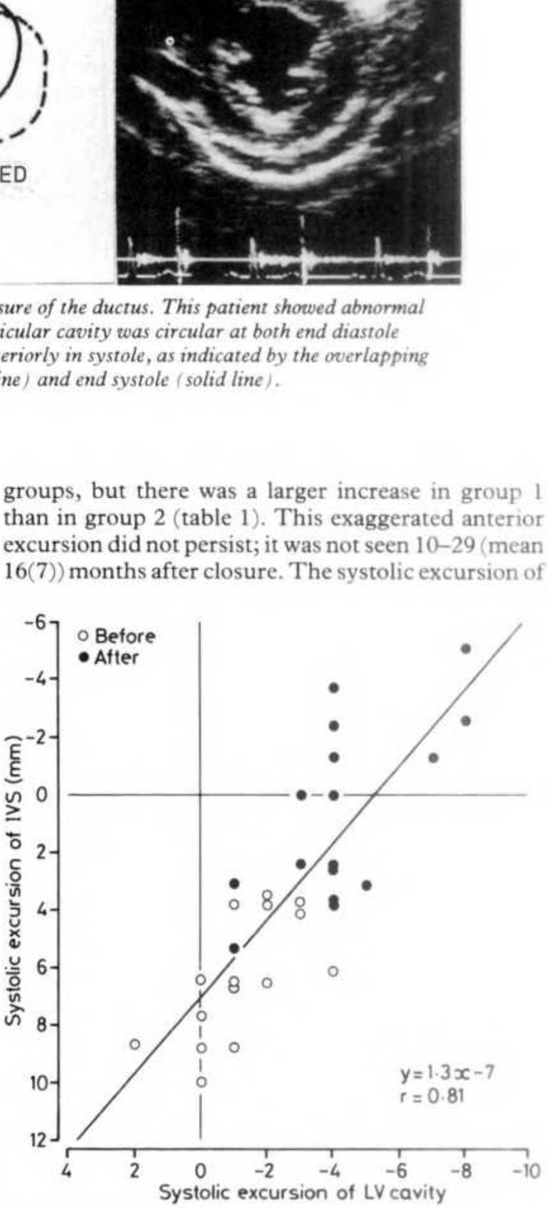

Fig 5 *Relation between the systolic excursion of the ventricular septum (IVS) and that of the left ventricular cavity before (○) and soon after closure of the ductus (●) in all patients examined. The linear correlation ($r = 0{\cdot}81$) was statistically significant ($p < 0{\cdot}01$).*

the interventricular septum was closely correlated with that of the centre of the heart before and after closure ($y = 1{\cdot}3x - 7$, $r = 0{\cdot}81$) (fig 5). Thus the abnormal septal motion was clearly caused by the exaggerated anterior motion of the heart.

Discussion

Septal motion can be abnormal in several conditions. It develops after therapeutic closure of the ductus[20] but the mechanism for this phenomenon is not clear. Catheter plugging is a non-surgical method of closing the ductus arteriosus.[17 18] The procedure does not cause intraventricular conduction disturbances, pericardial adhesion, or myocardial ischaemia, which may all cause abnormal septal motion. After closure of the patent ductus abnormal septal motion develops despite relief of abnormal hemodynamic function and disappears spontaneously some time later. We found that the abnormal septal motion in the present cases was a consequence of an anterior swinging motion of the heart and we have sought an explanation for this.

The severity of left ventricular volume overload before closure of the ductus is one possible explanation. The larger the left ventricular cavity before closure, the greater was the extent of abnormal motion after closure. Enlargement of the left ventricular and left atrial cavities owing to the ductus was significantly and rapidly reduced to normal by closure of the ductus. This acute change was associated with the development of abnormal septal motion.

Perhaps the reduction in size of the left heart induces relative right ventricular volume overload, which can cause abnormal septal motion. This is unlikely, however, because in our cases the right ventricular diameter was similar in the two study groups and the left ventricular cavity was almost circular in every patient. Deformation of the left ventricular cavity causes abnormal septal motion in patients with right ventricular volume overload.[19]

Shrinking of the heart caused by an acute reduction of long-standing left ventricular volume overload may cause the anterior motion of the heart. This feature resembles the abnormal septal motion seen in congenital absence of the pericardium.[4] Cross sectional echocardiograms showed that this results from the exaggerated systolic anterior motion of the heart,[21 22] possibly attributable to excessive posterior movement of the heart during diastole in the absence of pericardial support. In addition, the short axis cross section of the left ventricle was circular in all phases of the cardiac cycle in congenital absence of the pericardium.[22] This was also characteristic of our patients with abnormal septal motion. The pericardium in a patient with ductus arteriosus may be stretched by the long-standing volume overload of the left ventricle. Closure of the ductus relieves the left ventricular volume overload and the heart rapidly becomes smaller. The pericardium, however, does not shrink as rapidly,[23] and it becomes lax. Movement of the heart without pericardial restraint results in a swinging motion of the heart, as it does when there is no pericardium. Because we saw abnormal septal motion for only a short period after closure of the ductus we think that gradual shrinkage of the pericardium to the size of the heart leads to the disappearance of the abnormal swinging motion that is manifested by the abnormal septal motion on the echocardiogram.

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A histological study of the atrioventricular junction in hearts with normal and prolapsed leaflets of the mitral valve

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SUMMARY The mitral annulus is the point at which the atrial and ventricular walls meet the base of the mitral valve cusps. The suggestion that a variant of this arrangement termed "disjunction" was associated with prolapse of the leaflets prompted examination of the mitral atrioventricular junctions in seven normal hearts and six with prolapse owing to floppy mitral valves. A complete cord-like ring of connective tissue that encircled the atrioventricular junction and into which the three components were inserted at the same point was found in only one heart. The remaining hearts all showed a mixture of segments in which either the three components were inserted into a cord or simply met. Disjunction, defined as a separation of the atrial wall-mitral valve junction from the other component, the left ventricular wall, can occur both with and without a cord-like annulus. There was no significant difference in the number of segments around the left atrioventricular junction which showed disjunction in hearts with normal or prolapsing leaflets.

The feature termed disjunction is an anatomical variation of the normal morphological characteristics of the left atrioventricular junction.

The pathogenesis of the floppy mitral valve remains controversial. Many theories have been advanced since Reid proposed a valvar origin for the mid-systolic click and late systolic murmurs.[1] Jeresaty argued[2] that there were two theories to account for floppiness of the mitral valve. The first emphasises the abnormality of the valve, whereas the second postulates myocardial involvement. Most morphological evidence accords with the suggestion that an abnormality of the valve is responsible for prolapse. Abnormality of the valve has been ascribed to a primary deficiency of the dense collagenous and fibrous layer of the leaflets[3–6] or an anatomical abnormality of the cords.[7 8]

A third possibility was proposed by Hutchins and his colleagues who suggested that a distinctive and basic anomaly of a floppy valve is disjunction of the fibrous annulus—that is a separation between the atrial wall-mitral valve junction and the left ventricular attachment.[9] They argued that this anomalous feature, through a process of hypermobility of the tension apparatus, could lead to floppiness of the leaflets. This group, however, studied only limited histological sections from a large number of hearts to demonstrate the significant association between so-called "disjunction" and floppy and prolapsed leaflets.

It seemed to us that it was important to test their hypothesis by examining in detail the entire atrioventricular junction in a smaller number of hearts. This report describes our findings.

Patients and methods

We examined 13 hearts obtained an necropsy. The mitral valve was normal in seven (from 3 men and 4 women) and floppy in six (from 4 men and 2 women). The specimens of normal hearts came from a group aged 66–80 years (mean 71·9) and those with floppy valves came from a group aged 56–89 years (mean 69·5). The valves were classified as "floppy" if they

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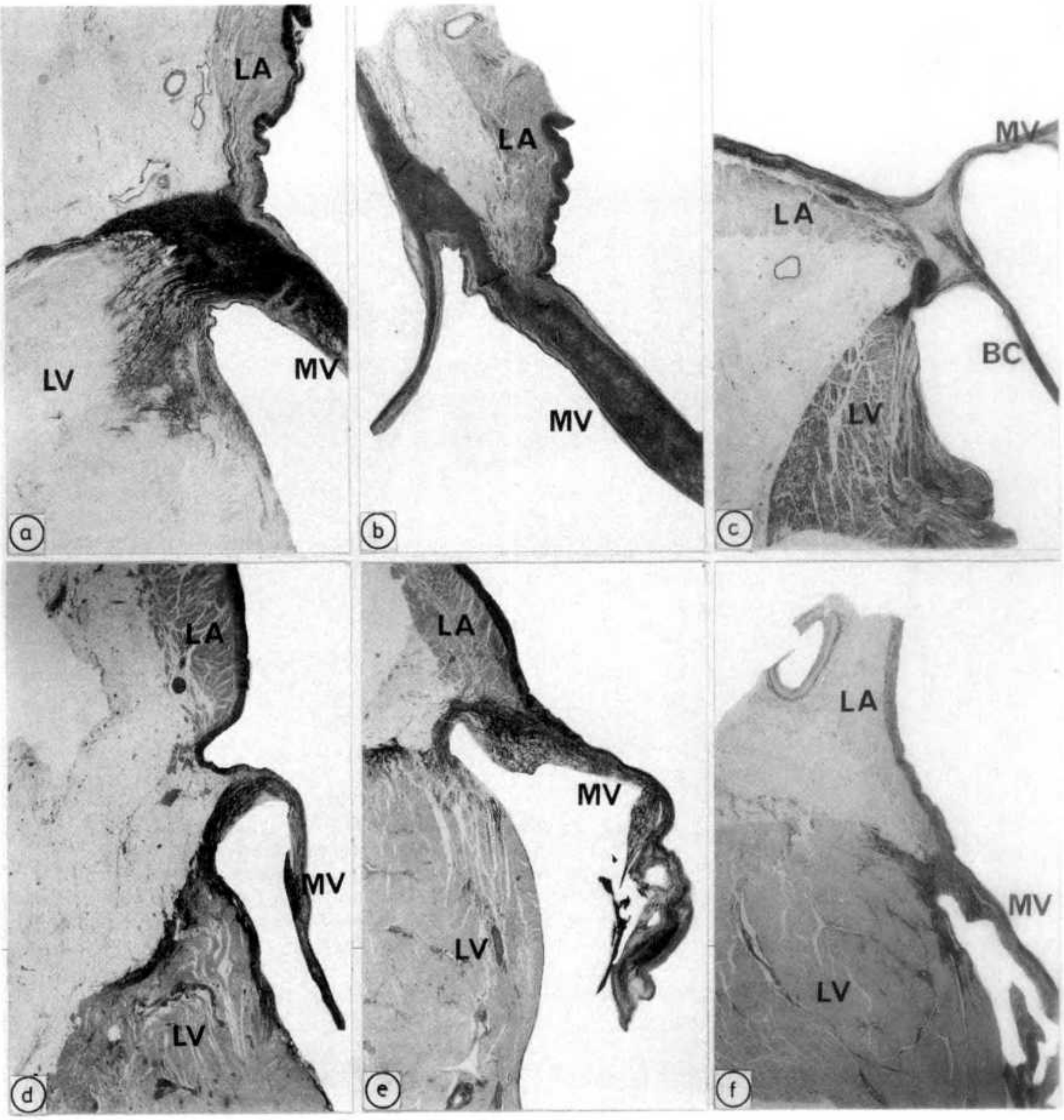

Fig 1 *Photomicrographs of sections showing structural variations in the left atrioventricular junction in hearts with normal leaflets of the mitral valve. The sections were cut perpendicularly to the atrioventricular junction. LA, left atrium; LV, left ventricle; MV, mitral valve. In (a) there is a cord-like annulus at the site of the left fibrous trigones whereas in (b) there is a fibrous continuity between the leaflets of the mitral and aortic valves. No dense fibrous aggregation resembling a cord-like annulus was detectable. In (c) a cord-like annulus supports the hinge of the leaflet from a basal tendinous cord (BC). (d) Shows a curtain-like annulus. The atrial myocardium stops short of the hinge. There is a curtain-like annulus in (e) too, where the atrial myocardium is inserted into the hinge of the leaflet. In (f) there is a curtain-like annulus attached below the apex of the ventricular wall. The arrangements seen in c, d, and e are all examples of so-called "disjunction" as defined by Hutchins* et al.[9] *Elastic-Van Gieson stain (original magnification,* × *10).*

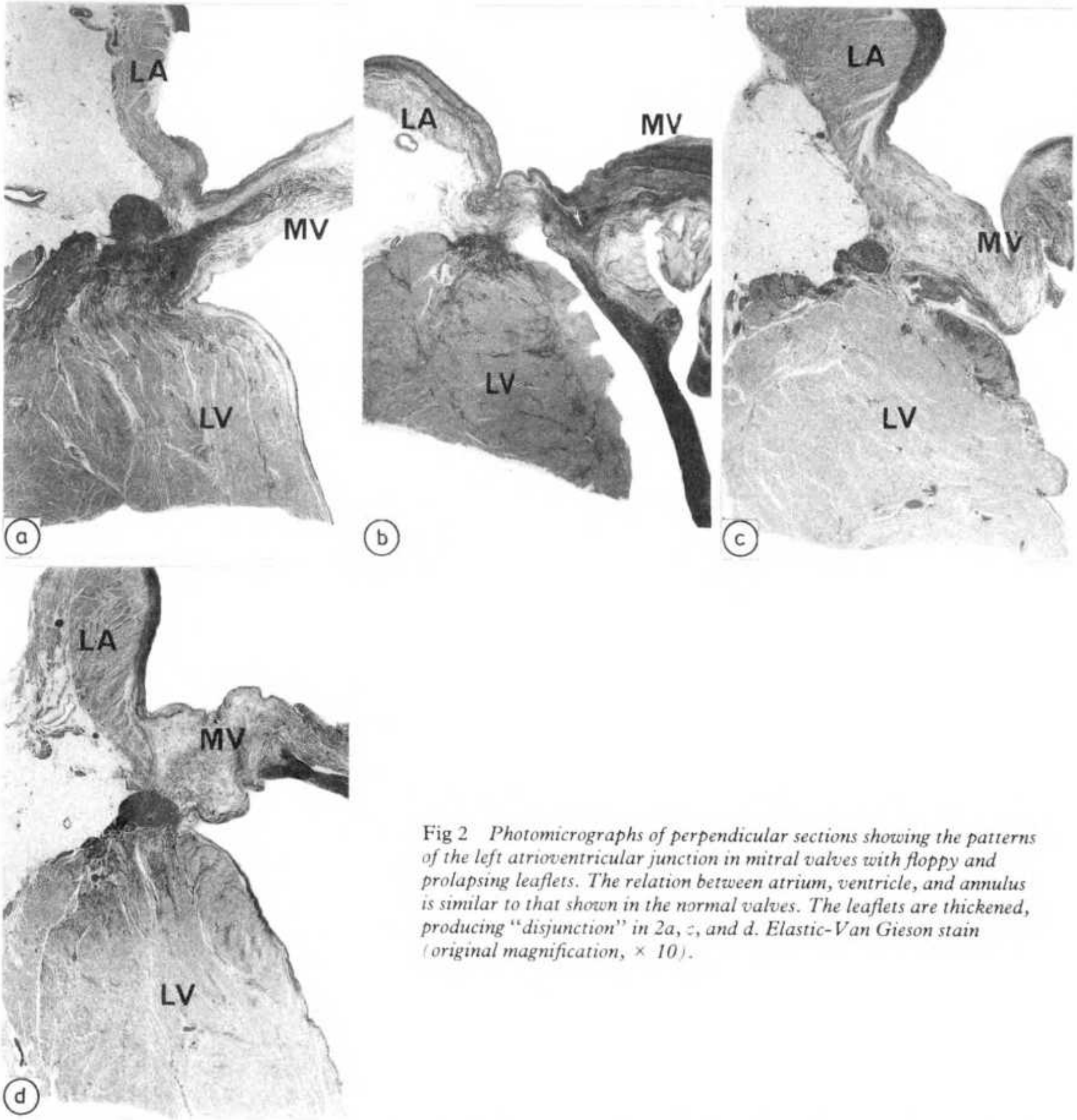

Fig 2 *Photomicrographs of perpendicular sections showing the patterns of the left atrioventricular junction in mitral valves with floppy and prolapsing leaflets. The relation between atrium, ventricle, and annulus is similar to that shown in the normal valves. The leaflets are thickened, producing "disjunction" in 2a, c, and d. Elastic-Van Gieson stain (original magnification, × 10).*

they were seen to have redundant leaflets with a dome-like expansion bulging into the left atrial chamber. The severity of the involvement of the leaflets varied. All the leaflets in all but one of the floppy valves were abnormal. In this specimen only the middle scallop of the mural leaflet was affected.

Serial sections were cut perpendicularly to the valve ring along the atrioventricular junction of each heart every 3 mm and stained with elastic-Van Gieson reagent. For each valve, we mapped the structure of the annulus and the presence of so-called "disjunction". Hutchins and colleagues defined disjunction as "a separation between the atrial wall-mitral valve junction and the left ventricular attachment".[9] We also described the fibrous support at the atrioventricular junction as cord-like or curtain-like according to its sectional structure. We have described the general region of attachment of the mural leaflet at the atrioventricular junction as the hinge regardless of whether a cord-like or a curtain-like fibrous aggregation was present. The area of fibrous continuity between aortic and mitral valves was excluded from analysis, since there is no hinge-like arrangement with the ventricular myocardium along

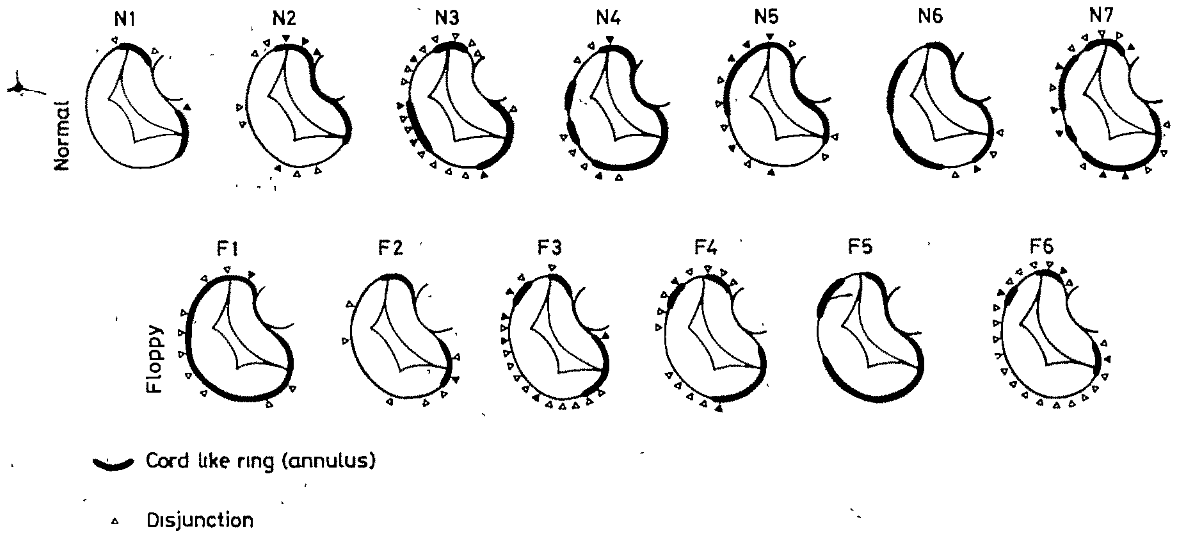

Fig 3 *Diagram showing the structural variations in the annulus around the left atrioventricular junction in all the valves studied. There is no significant difference between the number of segments showing so-called "disjunction" in the groups of hearts with normal and prolapsing leaflets.*

this segment of the junction.

Results

Examination of the histological sections showed considerable variation in the arrangement of the atrioventricular junction and in the relation of the structures making this junction, not only from heart to heart but within the same heart. Fig 1 shows the most common features:

Thick and well organised fibrous structures that produce a cord-like segment of ring are always present at the site of the left and right fibrous trigones. These are the thickened areas at the extremities of the region of fibrous continuity between the leaflets of the mitral and aortic valves. At the trigones, the aortic leaflet of the mitral valve hinges on the annulus with insertion of the atrial myocardium at the level of the hinge. The annulus itself is located at the apex of the ventricular myocardium (fig 1a). The area of fibrous continuity between the trigones is an extensive fibrous sheet joining the attachments of the two valves. Often no dense fibrous aggregation resembling a cord-like ring is detectable along this segment of valvar continuity (fig 1b). Threads of fibrous tissue occasionally extend laterally from each of the fibrous trigones and run posteriorly to embrace part of the orifice (fig 1c). In these areas, the atrial myocardium reaches the annulus, a basal tendinous cord supports the valve leaflet, and the hinge of the leaflet is displaced upwards. These extensions of cord-like fibrous tissue, none the less, do not extend as a continuous structure throughout the circumference of the valve. In most cases, the fibrous tissue of the annulus is organised in many segments of the "ring" as a thin curtain-like structure (fig 1d, 1e, and 1f). In many areas (fig 1d), the atrial myocardium stops short of the hinge of the leaflet, leaving adipose tissue to fill the gap. Alternatively, the atrial myocardium may be inserted into the hinge (fig 1e) or the annulus may be attached below the apex of the ventricular wall (fig 1f).

For the atrioventricular junction of the floppy mitral valves exactly the same range of variation is found as in normal hearts (fig 2). This holds true both for the site of abnormalities around the junction and for the type of collagenous aggregation (cord-like ring or curtain-like features). The only difference between normal and floppy valves was the presence of thickened leaflets in floppy valves. Figure 3 shows the variation in the morphology of the annulus from point to point around the junction of the hearts studied. So-called "disjunction", as defined by Hutchins and colleagues, was equally frequent in normal as in floppy valves (no significant difference as determined by Mann-Whitney test).

Discussion

Our results show that the arrangement in which a complete cord-like ring (or annulus) of connective tissue encircles the left atrioventricular junction and supports the leaflets of the mitral valve, at the same time separating the contiguous segments of atrial and ventricular myocardium, is exceptional. Such appearances were found at limited points around the junction of all the hearts we studied. No statistical difference could be detected between normal and floppy valves. The degree of collagen in the ring, especially in its curtain-like segments, varied from an easily identifiable structure as thick as the fibrous layer of the leaflets to a thin strand of fibres.

Variation in the relation of the structures making up the atrioventricular junction was another characteristic of the mitral valve. The relation between the atrial and ventricular myocardial segments at the junction seemed closer in the floppy than in the normal valve. Indeed, some of our cases of floppy valve demonstrated the feature defined by Hutchins and his colleagues as "disjunction".[9] It seems to us, however, that there is no displacement of the junction of the myocardial segments in these hearts. Rather, the apparent separation of atrial wall, valve leaflet, and ventricular myocardium ("disjunction") is produced solely by the thickness of the leaflets at the hinge. It is, therefore, difficult for us to accept the view that in floppy valves there is a significant association with "disjunction" of the atrioventricular junction.

It should be noted that in the study of Hutchins and his colleagues only one block was taken for histological examination from the obtuse margin of the mitral annulus of each normal heart.[9] This method probably accounts for the small percentage of "disjunction" found in the normal hearts studied by Hutchins *et al.*[9] We agree with Hutchins *et al* when they state that "disjunction" is an anatomical variation of the normal morphological characteristics of the mitral annulus,[9] as it is in floppy valves too. If hypermobility of the mitral apparatus is important in producing prolapse, it is probably produced by other abnormalities over and above so-called "disjunction".

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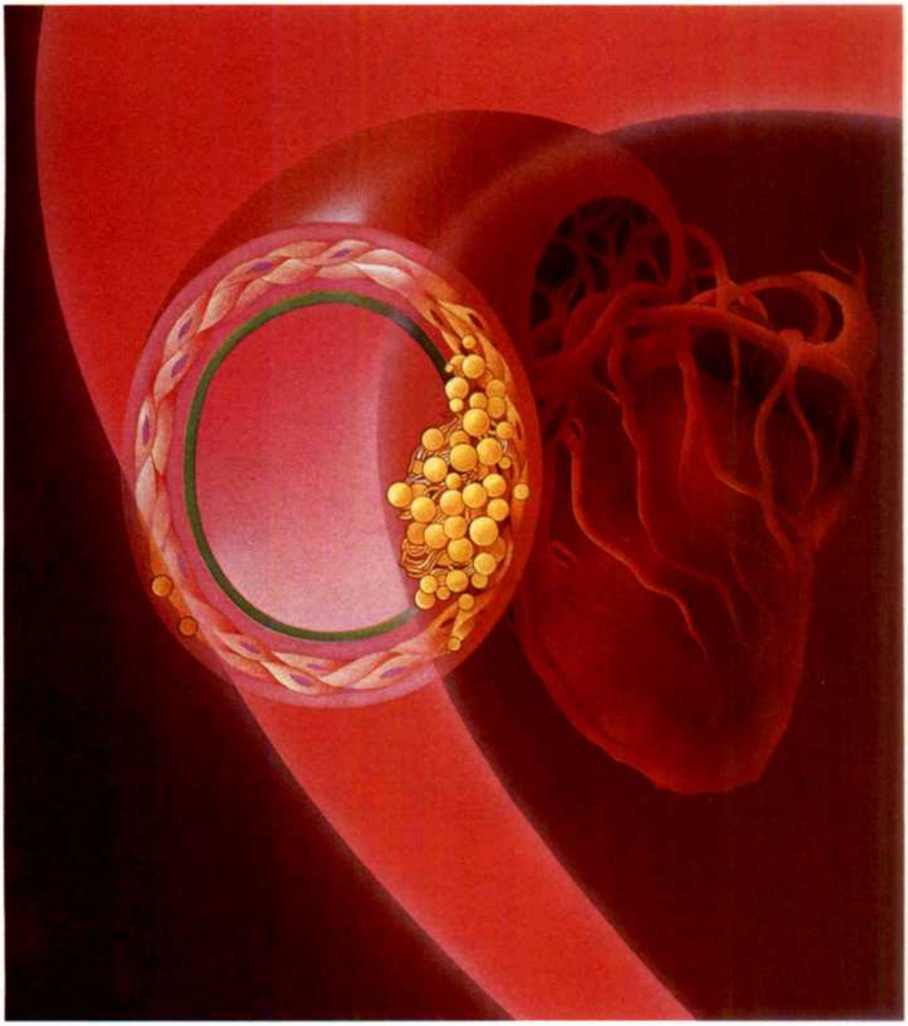

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Br Heart J 1988;59:717–20

Case reports

Two simultaneous right ventricular tachycardias in a case of arrhythmogenic right ventricular dysplasia

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SUMMARY A 51 year old woman with arrhythmogenic right ventricular dysplasia had two types of ventricular tachycardia—(*a*) a regular and sustained tachycardia and with normal frontal plane axis on electrocardiography and (*b*) an irregular non-sustained tachycardia with a leftward frontal plane axis. Changes in the QRS complex were sometimes seen during the sustained ventricular tachycardia. The clinical, electrocardiographic, and electrophysiological data were consistent with the diagnosis of two different and sometimes simultaneous tachycardias originating in the right ventricle.

This case suggests a possible new mechanism for the multiform appearances of the ventricular tachycardia.

Multiple forms of ventricular tachycardias are commonly found in patients with arrhythmogenic right ventricular dysplasia.[1 2] But the simultaneous occurrence of two separate ventricular tachycardias has not been reported before. We report a patient with arrhythmogenic right ventricular dysplasia and unusual multiform sustained and non-sustained ventricular tachycardias, both with a left bundle branch block configuration but normal (+45°) and leftward (−20°) frontal plane axis. The clinical, electrocardiographic, and electrophysiological data support the diagnosis of two different and sometimes simultaneous tachycardias both originating in the right ventricle.

Case report

A 51 year old woman had a three year history of untreated mild hypertension. For many years she had complained of occasional palpitation. The electrocardiogram in sinus rhythm was normal, with inverted T waves in V1 and V2 and flattening or mild inversion in V3, and isolated uniform extrasystoles with a left bundle branch block configuration. In August 1986 she was admitted to the coronary care unit with palpitation and hypotension; the electrocardiogram showed regular, sustained ventricular tachycardia (180/min) and left bundle branch configuration with a normal frontal plane axis (+45°) (fig 1a). Intravenous lignocaine (150 mg) was ineffective but a 150 J electrical shock restored the sinus rhythm.

The chest *x* ray was normal but the M mode and cross sectional echocardiography showed an abnormal trabecular pattern and regional dyskinesia of the inflow and apical segments of the right ventricle with generalised dilatation of the outflow tract. Few hours later brief episodes of non-sustained (4–5 QRS complexes), irregular, repetitive ventricular tachycardia were recorded at a rate of 110–130/min with left bundle branch block configuration and a leftward frontal plane axis (−20°) (fig 1b). On the second day, in the absence of drug treatment, the previous sustained ventricular tachycardia recurred; long electrocardiographic strips sometimes showed aberrations in the QRS complexes (generally in leads II, III, and aVF) that were characterised by gradual variations of the frontal plane axis from +45° to −20°, slight differences in the RR intervals, and fusion complexes (fig 2a). Intravenous flecainide (2 mg/kg) was given slowly and abolished the ventricular tachycardia.

The haemodynamic and angiographic investigation showed a right ventricular end diastolic volume of 100 ml/m², an end systolic volume of 68 ml/m²,

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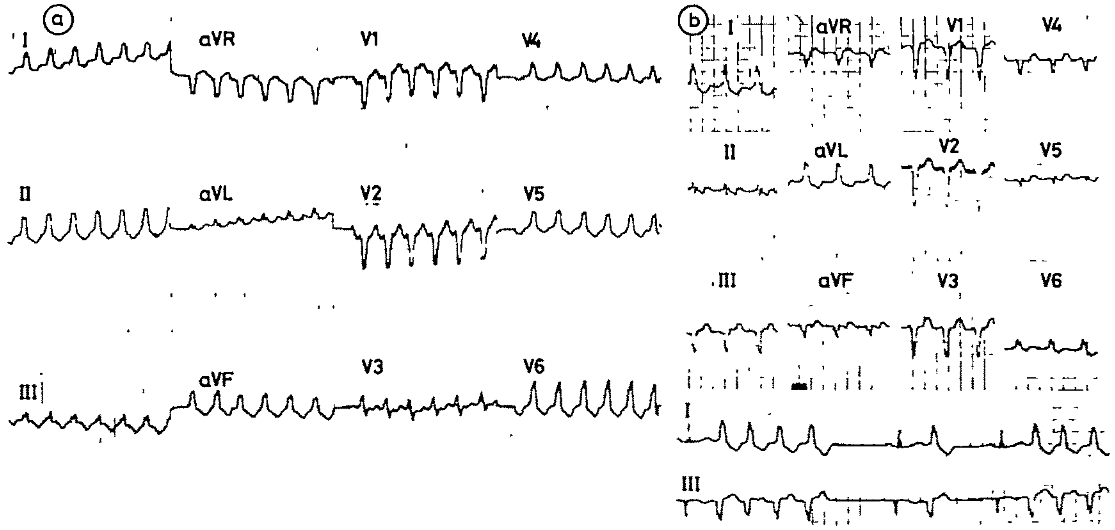

Fig 1 *(a) Electrocardiogram showing regular sustained ventricular tachycardia at a rate of 180 beats/min with left bundle branch configuration and normal axis (+45°) (b) Electrocardiogram showing irregular non-sustained repetitive ventricular tachycardia at a rate of 110–130 beats/min with left bundle branch configuration and a leftward frontal plane axis of −20° The electrocardiographic strip of I and III shows the pattern of the ventricular tachycardia.*

and an ejection fraction of 32%; structural alterations of the trabecular zone, hypokinesia of the inferior and apical wall, bulging of the inflow tract, and infundibular dilatation were also present. The left ventricle was normal.

At electrophysiological study the basal intervals were normal (PA = 35 ms, AH = 100 ms, HV = 40 ms). Delayed and fractioned electrical potentials were recorded from the right ventricular outflow tract. Clinical non-sustained ventricular tachycardia with a leftward frontal plane axis appeared spontaneously, and a complete catheter electrode endocardial mapping, performed in eight different sites in the right ventricle, showed that electrical activation started in the right ventricular apex (fig 2b). Furthermore, sustained ventricular tachycardia with a normal frontal plane axis was easily induced by right ventricular extrastimuli during ventricular drive at 600 ms with coupling intervals for S1–S2 of 280 ms to the right ventricular refractory period (220 ms). Accurate catheter electrode endocardial mapping showed that electrical activation started in the right ventricular outflow tract (fig 2b). In addition, during the induced clinical sustained ventricular tachycardia, the previous alteration of the QRS complexes appeared spontaneously, and catheter electrode endocardial mapping showed a simultaneous early electrical activation in both the right ventricular apex and outflow tract (fig 2b). Right ventricular overdrive at a cycle length of 300 ms or a bolus of intravenous flecainide restored the sinus rhythm during sustained tachycardia but not during non-sustained ventricular tachycardia, which reappeared after the infusion. Also, after flecainide right ventricular incremental pacing—with two or three premature stimuli during three different ventricular drives, and bursts, delivered to either the right ventricular apex or right ventricular outflow tract, did not induce the sustained ventricular tachycardia. Oral flecainide (200 mg/day) was given but at a follow up on 24 hour Holter monitoring sporadic episodes of the non-sustained ventricular tachycardia persisted. Treatment with amiodarone (1000 mg/week) was successful and 12 months later she was free of symptoms and arrhythmias.

Discussion

This patient with arrhythmogenic right ventricular dysplasia that affected the apex and the inflow and the outflow segments of the right ventricle may be described as having pleomorphic ventricular tachycardia.[1] But she was unusual in having two types of ventricular tachycardia: (*a*) a sustained ventricular tachycardia with normal frontal plane axis and (*b*) an irregular, non-sustained, repetitive ventricular tachycardia with a leftward frontal plane axis that was not corrected by intravenous flecainide. Electrocardiographic strips recorded during the sustained ventricular tachycardia sometimes showed a gradual shift of the QRS axis from normal to left axis

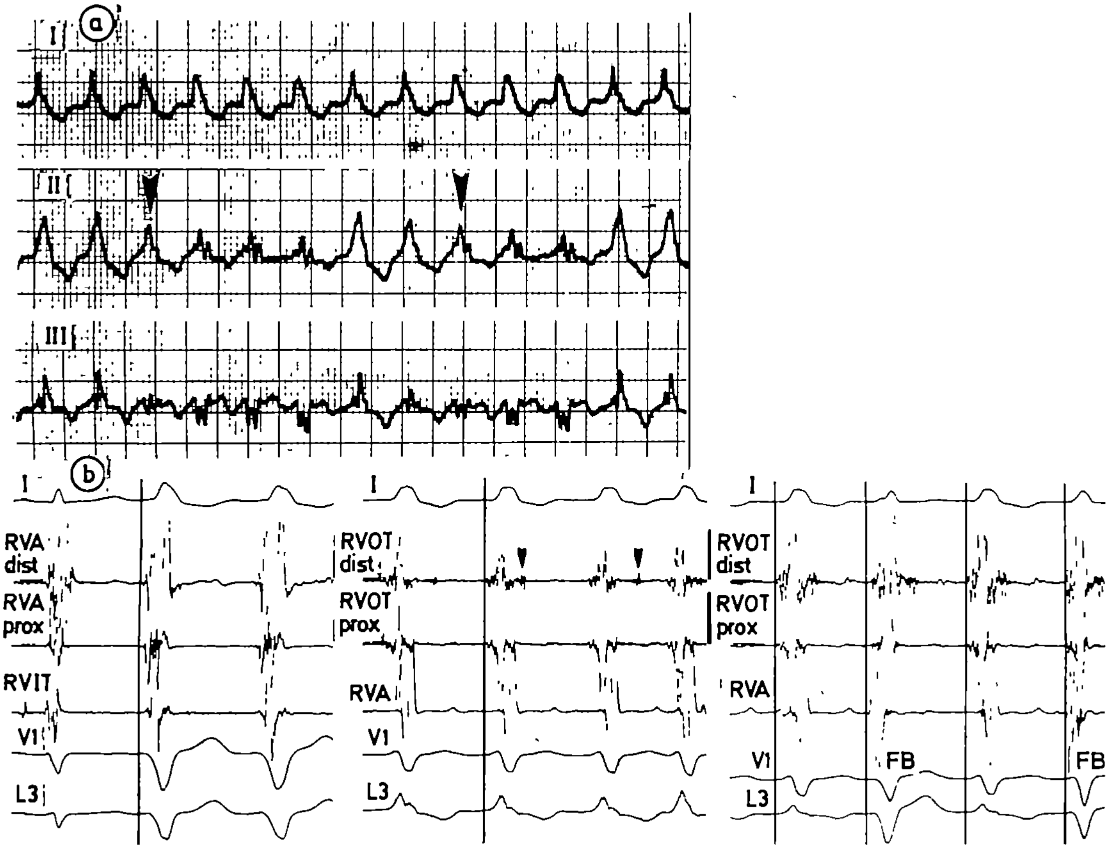

Fig 2 *(a) Electrocardiographic trace of leads I–III during the spontaneous sustained ventricular tachycardia. Note the shift of frontal plane axis, the slight change in RR intervals, and the presence of fusion beats (arrows). (b) Spontaneous non-sustained ventricular tachycardia (left panel), the clinical sustained ventricular tachycardia induced by ventricular stimulation (middle panel), and the spontaneous alteration of the QRS complex (see fig 2a) recorded during the sustained ventricular tachycardia (right panel). Top to bottom. lead I, electrograms from the right ventricular apex (RVA distal and proximal electrodes), the right ventricular inflow tract (RVIT), the right ventricular outflow tract (RVOT distal and proximal electrodes), and VI and III. The earliest electrical activation was recorded in the RVA (left panel) and in the RVOT (middle panel). In the right panel, during the pleomorphism, the earliest activation changes were recorded in the RVOT in the first and the third beat, in the RVA (nearly simultaneously) in the second beat, and simultaneously (RVA and RVOT) in the fourth FB, fusion beat. Late fractioned electrical potentials were recorded in RVOT (arrows). The vertical lines mark the onset of the earliest endocardial electrograms. Note that in each panel the electrograms precede the onset of the surface QRS complex Paper speed 100 mm/s.*

deviation, slightly irregular RR intervals, and fusion beats.

Our case resembles a case reported by Strasberg *et al* who found ventricular tachycardia with right bundle branch block and right and left axis deviation in opposite directions[3]. In the absence of electrophysiological data they suggested that their patient had two separate foci or a common focus, within or close to the left bundle branch, with different exit pathways and different electrophysiological properties. In our case the clinical and electrocardiographic behaviour and the response to the electrical stimulation and to flecainide strongly support the presence of two different electrophysiological mechanisms. Moreover, the results of endocardial catheter electrode mapping clearly showed that the two tachycardias had separate origins.

Another unusual feature of our case was the occurrence of alterations in the QRS complexes during sustained ventricular tachycardia. Electrophysiological mapping of the right ventricle showed the simultaneous onset of ventricular activation in both the apex and outflow tract, and this is further evidence that the two different tachycardias occurred together. As far as we know, mapping has never shown this feature before. Nevertheless, we cannot exclude the possibility of a single site of origin with different routes of impulse propagation and the simultaneous arrival of impulses at the apex and outflow tract. Our case shows that there can be widespread involvement of the right ventricle even when the heart silhouette is normal and there are no important clinical signs; this suggests a possible new mechanism for the multiform appearances of the ventricular tachycardia.[4]

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Congenital diverticulum of the right atrium situated on the floor of the coronary sinus

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SUMMARY A diverticulum of the right atrium was found on the floor of the coronary sinus in a neonate. The diverticulum was distinguished from a pericardial cyst by contrast echocardiography, and its relations with coronary sinus and coronary venous return were identified by coronary angiography. Because the diverticulum compressed the left ventricular inferior wall and prevented its growth, it was excised. Thebesian veins were discovered at operation and prevented complete correction of the defect.

Congenital diverticula of the right atrium are rare anomalies, whereas idiopathic dilatation of the right atrium is more commonly reported. The coronary sinus may sometimes be slightly enlarged if it is receiving a left superior vena cava or total anomalous pulmonary venous return. Sizeable dilatation of the coronary sinus is uncommon and has been reported only once before.[1] In this case, the right superior vena cava was absent, the persistent left vena cava drained the whole superior venous flow; the patient was symptom free.

We report on a diverticulum that we found at an unusual site in a neonate. To our knowledge this is the second case of this anomaly to be described and the first one in which an operation was performed.

Case report

A 3 kg baby boy was born by caesarean section after a 37th week twin gestation. He had talipes, and a precordial murmur was heard when he was 10 days old. His brother was normal. The patient was referred to the pediatric cardiology unit. Physical examination showed a symptom free baby without cyanosis, with a grade 4/6 pansystolic murmur and a single normal second heart sound. Chest radiography showed slight enlargement of the heart with a bulge from the right atrium and a slight prominence of the pulmonary vasculature. The electrocardiogram showed left axis deviation of 45°, an incomplete right bundle branch block, and a QS feature in leads II, III, and aVF. Echocardiography and pulsed Doppler were performed. We found a small perimembranous ventricular septal defect and an ostium secundum. But the most striking discovery was the presence of a large cavity behind the posterior wall of the left ventricle. In the parasternal long axis view, this pouch seemed to reduce the tranverse diastolic diameter of the left ventricle, which measured only 18 mm (fig 1a). In the subcostal view, this pouch could be seen to extend down to the inferior aspect of the heart (fig 1b). Because Doppler echocardiography did not detect any flow within this cavity, it was impossible to say whether the pouch was connected to any of the heart cavities or whether it was a pericardial cyst. Contrast echocardiography was performed after injection of dextrose into a left antecubital vein. Contrast echoes entered the right atrium immediately and then were quickly seen in the pouch, but never in the coronary sinus. This showed that the left superior vena cava had not persisted. A posterior diverticulum of the right atrium was diagnosed.

During the next few months the boy grew normally and remained symptom free. The ventricular septal defect closed spontaneously when he was six months old. But repeat echocardiograms showed that the size of the pouch remained the same and seemed to prevent growth of the left ventricle. When he was eight months old the ventricle was the same size as in the neonatal period and left ventricular filling was shown to be abnormal by pulsed Doppler examination. The peak velocity of atrial systole equalled that in early diastole. Cardiac catheterisation was performed when he was nine months old. Pressures inside the right cavities were normal. A left to right shunt was found only at the atrial level (QP/QS = 2). In the

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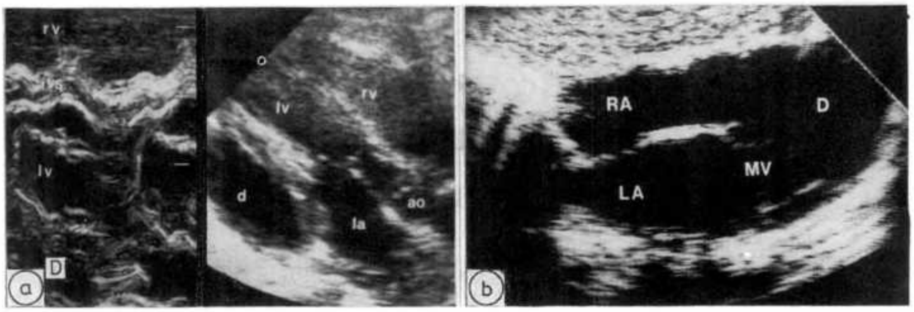

Fig 1 *(a) M mode and cross sectional echocardiograms in the parasternal long axis view. The diverticulum lies behind the left ventricle. (b) Cross sectional subcostal view through the inferior part of the heart into which the diverticulum extends. D, d, diverticulum; rv, right ventricle; lv, left ventricle; la, left atrium; ao, aorta; MV, mitral valve; RA, right atrium.*

right atrium the catheter could be passed from the top to the floor through an atrial septal defect, through the tricuspid valve, and into a cavity in the left side of the chest in the anteroposterior view. The coronary sinus and left superior cava were not entered. The pressure and oxygen content of blood were the same in this pouch as in the middle of the right atrium. Left ventricular end diastolic pressure was normal (10 mm Hg). Angiography showed that the diverticulum lay below and behind the heart and communicated with the right atrium through a large opening (fig 2a). Left ventricular injection confirmed the restriction of the posterior wall, the position of which was abnormally high (fig 2b). There was no evidence of a connection between the right ventricle and the pouch. An intracardiac electrocardiogram was performed to locate the electrophysiological pathways. There was no anomaly either in the right atrium or in the right ventricle. A QS feature was recorded inside the diverticulum as well as at the inferior wall of the heart. This feature was identical with the same QS feature in surface leads II, III, and aVF.

The anatomy of the coronary sinus was studied by selective coronary angiography. The coronary veins drained normally into the coronary sinus, which was not enlarged and overhung the opening of the diverticulum inside the right atrium.

Surgical correction was undertaken at the age of 11 months. The diverticulum was found to extend over

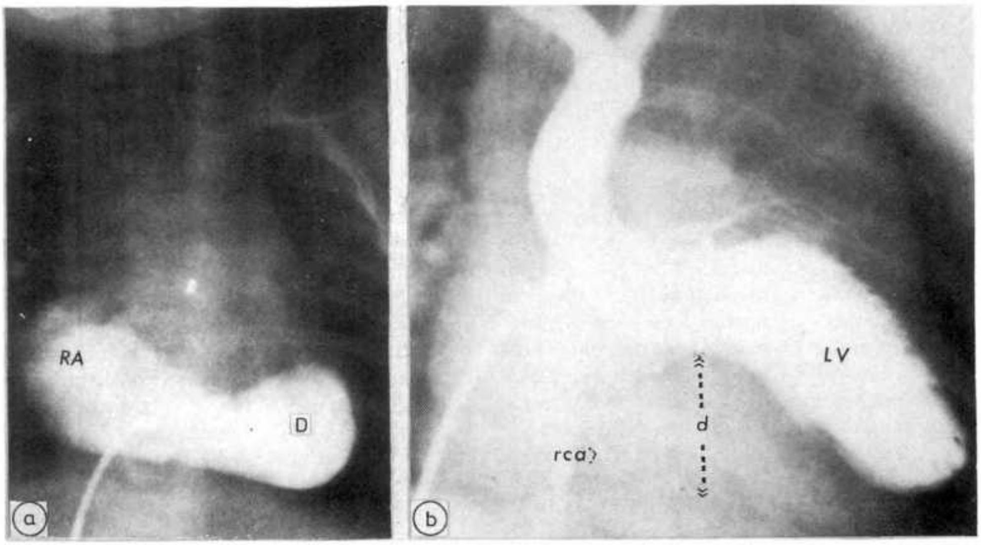

Fig 2 *Cineangiograms showing (a) anteroposterior view after injection of contrast into the diverticulum and (b) 30° right anterior oblique view of the left ventricle, which is raised up by the diverticulum which lies between the posterior wall of the ventricle and the right coronary artery (rca).*

all the diaphragmatic area of the heart. There was a 1 cm diameter opening between the tricuspid valve and the ostium of the inferior vena cava. Some thebesian veins drained into the inlet of the pouch and therefore prevented complete closure of the defect at operation. The distal four fifths of the diverticulum were closed by resection of the redundant tissue and with a padding suture. The atrial septal defect was then closed. At the end of the operation a tiny cavity remained at the junction between right atrium and left ventricle inferior wall to receive the coronary sinus and thebesian veins. Histological examination of the diverticulum wall showed that it was made of normal atrial tissue.

The postoperative course was uneventful. Three months later physical examination was normal. The radiographic enlargement of the heart had decreased. The electrocardiogram showed that the QS feature in the frontal leads had disappeared and the electrical axis view had become perpendicular to the frontal plane. Echocardiography in parasternal long axis view showed the absence of the cavity and that the left posterior wall adjoined the pericardium. The subcostal view showed a tiny pouch behind the tricuspid valve and the interventricular septum. Examination by pulsed Doppler showed that left ventricular filling was normal and that the diameter of the ventricle in diastole had increased to 30 mm.

Discussion

This diverticulum developed at the junction between the coronary sinus and the right atrium. We have found only one similar case in published reports.[2] It was of a neonate with a hypoplastic left ventricle who died at the age of four days. The echocardiogram and necropsy showed a large diverticulum behind the left side of the heart with an opening on the floor of the coronary sinus into which a left superior vena cava drained.

The explanation for the diverticulum may lie in embryological development. The right Cuvier's canal becomes the right superior and inferior vena cavae while the left canal usually regresses after the fourth week of pregnancy to become the coronary sinus or sometimes a persistent left superior vena cava.[3] In Di Segni's case, as in ours, incomplete regression of the left Cuvier's canal may explain the presence of a retrocardiac pouch. Furthermore, the hypoplastic left ventricle in Di Segni's case and the failure of our patient to thrive suggest that such a diverticulum causes compression and leads to underdevelopment of the left ventricle. This is why we recommended early excision of the diverticulum.

Another possible site for a diverticulum of the right atrium is anterior, on the appendage. There is one report of such a case, in which an enormous diverticulum covered the anterior side of the heart, and caused severe episodes of arrhythmia when the patient was 16. The cavity contained a thrombus and the patient recovered after its removal.[4]

We would expect the prognosis when a diverticulum is present to resemble that of idiopathic dilatation of the right atrium, which is a more common condition. The parietal wall of a diverticulum contains normal amounts of atrial muscle fibres, as in our case, or slightly reduced amounts,[4] but in idiopathic dilatation of the right atrium the parietal tissue is almost devoid of muscle fibres.[5] Although it was initially regarded as benign, idiopathic dilatation has been found to be associated with congestive heart failure,[6] arrhythmias,[7] and sudden death.[8]

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Echocardiographic diagnosis of multiple congenital aneurysms of the sinus of Valsalva

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SUMMARY Aortic regurgitation developed in a 56 year old man with severe nephrotic syndrome. Cross sectional echocardiography showed bilateral aneurysms of the sinus of Valsalva and a bicuspid aortic valve. He died of intercurrent pneumonia. Postmortem examination confirmed the presence of the congenital aneurysms.

Congenital aneurysm of the sinus of Valsalva usually affects only one aortic sinus; however, cases of multiple congenital aneurysms of the sinus of Valsalva have been reported.[1] Cases of acquired aneurysm are seen in endocarditis and syphilis. Several reports have suggested that aneurysms of the sinus of Valsalva can be diagnosed by echocardiography.[2,3]

We report a case of congenital bilateral aneurysms of the sinus of Valsalva in a patient with a bicuspid aortic valve.

Case report

A 56 year old man presented with a one week history of ankle and facial swelling. He had a short history of anorexia and had lost a few pounds in weight.

On examination he looked well. His blood pressure was 110/60 mm Hg and he had a grade 2/6 early diastolic murmur in the aortic area. The jugular venous pressure was not raised. He had pitting oedema of the ankles and dipstick testing of his urine showed that it contained blood and a large amount of protein.

The diagnosis of an acute nephritis associated with the nephrotic syndrome was confirmed (serum urea 29·9 mmol/l and creatinine 260 μmol/l and urinary protein excretion 58 g/l). Immunological studies including immunoglobulin and complement concentrations and antinuclear factor antibodies were normal. A renal biopsy specimen showed changes of focal segmental glomerulosclerosis.

Repeated sets of blood cultures were negative for bacteria and fungi. The electrocardiogram showed left ventricular hypertrophy and his chest *x* ray showed moderate cardiomegaly.

Cross sectional echocardiography was performed with a Hewlett Packard 77020A real time phased array scanner. It showed a bicuspid aortic valve that was thickened and calcified. The excursion of the aortic valve was impaired. The parasternal sagittal view (figure a) showed bilateral aneurysms of the sinus of Valsalva. The first aneurysm, which was 2 cm in diameter, arose from the right coronary sinus and protruded into the right ventricular outflow tract. The second aneurysm arose from the left coronary sinus and protruded into the left atrium. The left ventricle was moderately hypertrophied and there was a small pericardial effusion.

Surgical correction of these aneurysms was prevented by the renal failure and massive protein loss (up to 80 g/day). After therapeutic renal artery embolisation he was maintained on regular haemodialysis, but a pneumococcal pneumonia developed and he died.

At necropsy the left ventricular hypertrophy and the presence of a bicuspid aortic valve were confirmed. The valve cusps showed fibrocalcific thickening and mild stenosis. There were bilateral aneurysms of the sinus of Valsalva (figure b). Both had a fibrous wall, contained organising blood clot, and communicated with the sinus via a defect lying between the cusp insertion and the coronary artery ostium. The right aneurysm of the sinus of Valsalva measured 2·5 × 1·5 × 3·0 cm and lay between the aortic root and the pulmonary infundibulum, with extension into the upper intraventricular septum. There was a rupture, 1·8 cm in diameter, through to the subvalvar area. The left aneurysm of the sinus of Valsalva measured 2·0 × 1·0 × 2·8 cm and lay between the aortic root, left atrium, and left atrial

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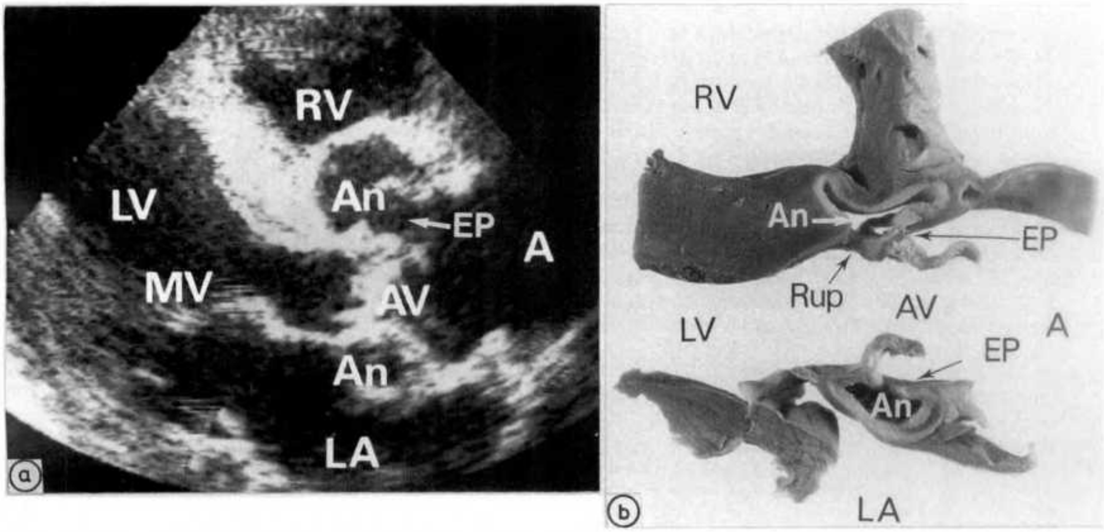

Figure *Parasternal long axis echocardiographic view (a) and section (original magnification × 1·2) (b) through the left ventricular outflow tract showing two aneurysms (An) of the sinus of Valsalva with rupture (Rup) of the right aneurysm into the left ventricle (LV). EP, entry points of aneurysms; A, aorta; RV, right ventricle; LA, left atrium; MV, mitral valve.*

appendage. Rupture through to the subvalvar area was incipient.

Discussion

Aneurysms of the sinus of Valsalva are rare. To date there have been 276 cases reported in English.[4-12] Such aneurysms often present after rupture in adult life. The diagnosis may be suspected from a history of abrupt onset of symptoms including dyspnoea, chest pain, or palpitation in the presence of a continuous murmur.[13] The mean age of presentation is 31 years. Most patients present with congestive cardiac failure and about 18% are symptom free at the time of detection. Aneurysms of the right sinus are frequently associated with a ventricular septal defect. The clinical manifestations of a ruptured aneurysm of the sinus of Valsalva depend on the direction and amount of blood flow through the abnormal intracardiac communication. The lesions are most commonly found in the right sinus and non-coronary sinus.[4] Perforation into the right sided cavities is more common; however, rupture may also occur into the left side of the heart, the pulmonary artery, the superior vena cava, the pericardium, and the intraventricular septum.[5,6]

In practice the diagnosis is usually confirmed at angiography; but several reports have shown that M mode and cross sectional echocardiography are valuable for non-invasive diagnosis.[6-8] Rupture of an aneurysm into either the right ventricular outflow tract or to the right atrium has been seen in parasternal views.[6] In our patient the aortic sinuses from which the aneurysms originated could be identified on parasternal views, and a possible rupture into the left ventricle was noted. Unfortunately, Doppler echocardiography, which would have been of great value in confirming the presence of a communication between the aneurysm and the left ventricle, was not available to us at the time of the examination.

Aneurysms of the sinus of Valsalva arising from bicuspid aortic valves are very rare—only five cases have been reported,[4,9,10] and rupture of a right sided aneurysm of the sinus of Valsalva into the left ventricle has been reported in only three cases.[12] We believe that ours may be the first report to describe the echocardiographic features of multiple congenital aneurysms of the sinus of Valsalva.

We thank Dr D H Bennett for his constructive criticism during the preparation of this paper.

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Br Heart J 1988;**59**:727–8

Correspondence

Da Costa's syndrome or neurocirculatory asthenia

Sir,

Da Costa's syndrome or its major physiological elements are common in patients with normal coronary arteries and in coronary arterial disease,[1-3] and their management lies in the province of cardiac rehabilitation. From the therapeutic point of view it is surprising to find Dr Paul (1987;**58**:306–15) omitting some of the most important considerations. For example, he does not refer to the extensive work that has given a leading aetiological role to hypocapnia and respiratory alkalosis.[4,5] Failure to recognise this role of hyperventilation is an error: its neglect prevents a rational approach to the dynamic factors that are capable of reducing the coronary circulation,[1-3] it invites a needlessly high surgical referral rate,[3] and takes away the possibility of dealing with a major cause of illness behaviour after myocardial infarction.[1-3]

The exhaustion factor so well known to Thomas Lewis and James Mackenzie requires treatment because it promotes high levels of arousal and sympathetic nervous activity that are aggravated by hyperventilation, together with habituation defects, limbic dysfunction, and disturbed activity of the left cerebral hemisphere.[6,7] The high levels of arousal interfere with sleep, reduce anabolic opportunities,[2] and lower the threshold for angina pectoris.[2] Defective habituation encourages the heart rate, the blood pressure, and other neuroendocrine responses to stimuli to become "undamped" and excessive, and thereby reduces the capacity for effort. The patient's furious struggling to keep up a customary range of activities perpetuates the arousal and increases the disabilities.[8]

We believe that the cardiac rehabilitation programme should accommodate these physiological factors and pay close attention to sleep, arousal, the breathing, the balance of rest and effort, and the self-esteem of the patient (acronym, SABRES).[2,9]

Reassurance does not have a longlasting effect upon the physiological degradation caused by hyperventilation and disordered habituation, nor can physical training restore high level fitness and stamina where performance is undermined by sleep loss, hyperarousal, hyperventilation, exhaustion, and loss of self esteem from seemingly endless cycles of frustration and defeat.

Dr Paul's recommendations sound uncomfortably like those that obtained no more than a 15% recovery rate in the era before we learned about hyperventilation and habituation.

Jenny C King,
P G F Nixon,
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This letter was shown to the author, who replies as follows:

Sir,

I thank Miss King and Dr Nixon for their comments on my review of Da Costa's syndrome (1987;**58**:306–15).

Their first concern is to emphasise the "leading aetiological role" of hyperventilation with hypocapnia and respiratory alkalosis in this syndrome. I agree that most patients with this condition complain of breathlessness, some may sigh intermittently, and a few may hyperventilate chronically. (Comroe defines hyperventilation as "alveolar ventilation in excess of that needed to eliminate metabolically formed CO_2".[1]) Unfortunately, as the reports cited both in my review and in the above letter indicate, although there have been excellent descriptions of physiological and clinical abnormalities resulting from hyperventilation (as defined by Comroe), it has not been possible to equate these with Da Costa's syndrome. Most patients with the syndrome do not hyperventilate chronically, their blood studies do not reveal consistent alkalosis, and essentially they never show the signal features of full-blown hyperventilation—that is numbness and tingling of the hands, feet, mouth, and tongue, spasms of the hands and feet, twitching, and finally convulsions. The whole issue was discussed by Paul Wood who wrote "the total evidence indicates that hyperventilation cannot be held responsible for the symptoms and signs of Da Costa's syndrome, neither by causing tissue alkalosis nor by interfering with the circulation; but it does occur in some, and when present must aggravate certain of the symptoms".[2] I find no reason with the passage of 47 years to differ with these conclusions.

Their second comment calls attention to exhaustion and its complications. I agree that there has been solid support for the role of exhaustion in certain patients, especially during wartime conditions.

Their third group of remarks relates to rehabilitation and treatment and in general I also concur with these, although I have found reassurance to be extremely helpful, and indeed critical.

Oglesby Paul,
Countway Library of Medicine,
Harvard Medical School,
10 Shattuck Street,
Boston, Mass 02115,
USA.

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Notices

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 22 to 24 November 1988. The closing date for receipt of abstracts has been changed to 24 June 1988 and is not as indicated in an earlier notice

The Annual General Meeting for 1989 will take place in Oxford on 6 and 7 April 1989, and the closing date for receipt of abstracts will be 6 January 1989.

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The 2nd International Symposium on Lasers in Cardiovascular Diseases will take place in Vienna on 3 and 4 October 1988. Inquiries to Congress Secretariat: Cosmos Convention Service, PO Box 141, Vienna, Austria.

Br Heart J 1988;59:729–30

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Further inquiries can be directed to Mr. Roger Mee, Director of Cardiac Surgery telephone (03) 345 5200 or Mr. J. Kelly, Chairman of the Division of Surgery telephone (03) 345 5278. Applications should be sent to the undersigned by Friday, 29th July, 1988.

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